



(11) **EP 2 303 846 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention
of the grant of the patent:
29.04.2015 Bulletin 2015/18

(51) Int Cl.:
C07D 217/24 ^(2006.01) **A61K 31/472** ^(2006.01)
A61P 9/00 ^(2006.01) **A61P 27/00** ^(2006.01)
A61P 25/00 ^(2006.01) **A61P 37/00** ^(2006.01)

(21) Application number: **09768949.1**

(86) International application number:
PCT/EP2009/004421

(22) Date of filing: **19.06.2009**

(87) International publication number:
WO 2009/156100 (30.12.2009 Gazette 2009/53)

(54) **SUBSTITUTED ISOQUINOLINES AND ISOQUINOLINONES AS RHO KINASE INHIBITORS**

SUBSTITUIERTE ISOCHINOLINE UND ISOCHINOLINONE ALS RHO-KINASE-INHIBITOREN

ISOQUINOLINES ET ISOQUINOLINONES SUBSTITUÉES UTILISÉES COMME INHIBITEURS DE
RHO-KINASE

(84) Designated Contracting States:
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL
PT RO SE SI SK TR**
Designated Extension States:
AL BA RS

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(30) Priority: **24.06.2008 EP 08290606**
17.02.2009 US 153149 P

(43) Date of publication of application:
06.04.2011 Bulletin 2011/14

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(56) References cited:
WO-A-2007/012422 WO-A-2008/020081
WO-A-2008/077556

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- **IWAKUBO ET AL: "Design and synthesis of Rho
kinase inhibitors (II)" BIOORGANIC & MEDICINAL
CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol.
15, no. 1, 15 November 2006 (2006-11-15), pages
350-364, XP005764617 ISSN: 0968-0896**

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Description

[0001] The present invention relates to substituted isoquinoline and isoquinolinones, their preparation and their use in the treatment and/or prevention of diseases related to the inhibition of Rho-kinase and/or of Rho-kinase mediated phosphorylation of myosin light chain phosphatase.

[0002] Activation of a small GTPase RhoA upon agonist stimulation results in conversion of RhoA from the inactive GDP-bound form to the active GTP-bound form with a subsequent binding to and activation of Rho-kinase. Two isoforms, Rho-kinase 1 and Rho-kinase 2, are known. Rho-kinase 2 is expressed in vascular smooth muscle cells and endothelial cells. Activation of Rho-kinase 2 by the active GTP-bound RhoA leads to calcium sensitization of smooth muscle cells through phosphorylation-mediated inhibition of the myosin light chain phosphatase activity and thereby up-regulation of the activity of myosin regulatory light chain (Uehata et al., Nature 1997, 389, 990-994).

[0003] It is known that Rho-kinase is involved in vasoconstriction, including the development of myogenic tone and smooth muscle hypercontractility (Gokina et al. J. Appl. Physiol. 2005, 98, 1940-1948), bronchial smooth muscle contraction (Yoshii et al. Am. J. Resp. Cell Mol. Biol. 1999, 20, 1190-1200), asthma (Setoguchi et al. Br. J. Pharmacol. 2001, 132, 111-118; Nakahara et al. Eur. J. Pharmacol. 2000, 389, 103-106) and chronic obstructive pulmonary disease (COPD, Maruoka et al. Nippon Rinsho, 1999, 57, 1982-1987), hypertension, pulmonary hypertension (Fukumoto et al. Heart 2005, 91, 391-392, Mukai et al. Nature 1997, 389, 990-994) and ocular hypertension and regulation of intraocular pressure (Honjo et al. Invest. Ophthalmol. Visual Sci. 2001, 42, 137-144), endothelial dysfunction (Steioff et al. Eur. J. Pharmacol. 2005, 512, 247-249), angina (Masumoto et al. Circulation 2002, 105, 1545-47, Shimokawa et al. J. Cardiovasc. Pharmacol. 2002, 40, 751-761), nephropathy, including hypertension-induced, non-hypertension-induced, and diabetic nephropathies, renal failure and peripheral arterial occlusive disease (PAOD) (Wakino et al. Drug News Perspect. 2005, 18, 639-643), myocardial infarction (Demiryurek et al. Eur. J. Pharmacol. 2005, 527, 129-140, Hattori et al. Circulation 2004, 109, 2234-2239), cardiac hypertrophy and failure (Yamakawa et al. Hypertension 2000, 35, 313-318; Liao et al. Am. J. Physiol. Cell Physiol. 2006, 290, C661-668; Kishi et al. Circulation 2005, 111, 2741-2747), coronary heart disease, atherosclerosis, restenosis (Pacaud et al. Arch. Mal. Coeur 2005, 98, 249-254; Retzer et al. FEBS Lett. 2000, 466, 70-74; Negoro et al. Biochem. Biophys. Res. Commun. 1999, 262, 211-215), diabetes, diabetic complications, glucose utilization and metabolic syndrome (Sandu et al. Diabetes 2000, 49, 2178-2189; Maeda et al. Cell Metab. 2005, 2, 119-129), sexual dysfunction, e.g., penile erectile dysfunction (Chitale et al. Nature Medicine 2001, 7, 119-122), retinopathy, inflammation, immune diseases, AIDS, osteoporosis, endocrine dysfunctions, e.g. hyperaldosteronism, central nervous system disorders such as neuronal degeneration and spinal cord injury (Hara et al. J. Neurosurg. 2000, 93, 94-101), cerebral ischemia (Uehara et al. Nature 1997, 389, 990-994; Satoh et al. Life Sci. 2001, 69, 1441-1453; Hitomi et al. Life Sci. 2000, 67, 1929-1939; Yamamoto et al. J. Cardiovasc. Pharmacol. 2000, 35, 203-211), cerebral vasospasm (Sato et al. Circ. Res. 2000, 87, 195-200; Kim et al. Neurosurgery 2000, 46, 440-447), pain, e.g. neuropathic pain (Tatsumi et al. Neuroscience 2005, 131, 491-498; Inoue et al. Nature medicine 2004, 10, 712-718), infection of digestive tracts with bacteria (WO 98/06433), cancer development and progression, neoplasia where inhibition of Rho kinase has been shown to inhibit tumor cell growth and metastasis (Itoh et al. Nature Medicine 1999, 5, 221-225; Somlyo et al. Biochem. Biophys. Res. Commun. 2000, 269, 652-659), angiogenesis (Uchida et al. Biochem. Biophys. Res. Commun. 2000, 269, 633-640; Gingras et al. Biochem. J. 2000, 348, 273-280), vascular smooth muscle cell proliferation and motility (Tammy et al. Circ. Res. 1999, 84, 1186-1193; Tangkijvanich et al. Atherosclerosis 2001, 155, 321-327), endothelial cell proliferation, endothelial cell retraction and motility (Oikawa et al. Biochem. Biophys. Res. Commun. 2000, 269, 633-640), stress fiber formation (Kimura et al. Science 1997, 275, 1308-1311; Yamashiro et al. J. Cell Biol. 2000, 150, 797-806), thrombotic disorders (Kikkawa et al. FEBS Lett. 2000, 466, 70-74; Bauer et al. Blood 1999, 94, 1665-1672; Klages et al. J. Cell Biol. 1999, 144, 745-754; Retzer et al. Cell Signal 2000, 12, 645-648) and leukocyte aggregation (Kawaguchi et al. Eur. J. Pharmacol. 2000, 403, 203-208; Sanchez-Madrid et al. J. Immunol. 2003, 171, 1023-1034; Sanchez-Madrid, et al. J. Immunol. 2002, 168, 400-410), stem cell and induced pluripotent stem cell related biology, e.g. cell-cell interaction, proliferation, cell cycle progression, gene regulation, migration, actin cytoskeleton modulation, and related application, e.g. as viability, survival, recovery, growth, susceptibility toward apoptosis, differentiation, development, gene modulation, modulation of morphogenesis, hosting and invasion (Krawetz et al. BioEssay 2009, 31, 336-343; Claassen et al. Mol. Reprod. Dev. 2009, PMID: 19235204; Heng Tissue Cell 2009, PMID: 19261317; Arnsdorf et al. J. Cell. Sci. 2009, 122, 546-553, Kim et al. Stem Cells 2009, 27, 191-199), modulation of epithelial-mesenchymal transition (Royal et al. Mol. Biol. Cell 2000, 11, 1709-1725; Zondag et al. J. Cell Biol. 2000, 149, 775-782; Masszi et al. Am. J. Physiol. Renal. Physiol. 2003, 284, 911-924; Smallhorn et al. Development 2004, 131, 2641-2651; Wells et al. Cell Motil. Cytoskeleton 2005, 62, 180-194; Wu et al. Cancer Res. 2006, 66, 9527-9534; Fan et al. Mol Biol Cell. 2007, 18, 1083-1097; Cho et al. Cell Biol. Int. 2007, 31, 1225-1230; Giehl et al. Cells Tissues Organs. 2007, 185, 123-130; Rodrigues-Diez et al. Pharm. Res. 2008, 25, 2447-2461), and bone resorption (Chellaiah et al. J. Biol. Chem. 2003, 278, 29086-29097). Na/H exchange transport system activation (Kawaguchi et al. Eur. J. Pharmacol. 2000, 403, 203-208), Alzheimer's disease (Zhou et al. Science 2003, 302, 1215-1217), adducin activation (Fukata et al. J. Biol. Chem., 1998, 273, 5542-5548), and in SREB (Sterol response binding element) signalling and its effects on lipid

metabolism (Lin et al. Circ. Res. 2003, 92, 1296-304).

[0004] Therefore, a compound having inhibitory effect on Rho-kinase and/or on Rho-kinase mediated phosphorylation of myosin light chain phosphatase is useful for the treatment and/or prevention of cardiovascular and non-cardiovascular diseases involving Rho-kinase as the primary or secondary disease cause, like hypertension, pulmonary hypertension, ocular hypertension, retinopathy, and glaucoma, peripheral circulatory disorder, peripheral arterial occlusive disease (PAOD), coronary heart disease, angina pectoris, heart hypertrophy, heart failure, ischemic diseases, ischemic organ failure (end organ damage), fibroid lung, fibroid liver, liver failure, nephropathy, including hypertension-induced, non-hypertension-induced, and diabetic nephropathies, renal failure, fibroid kidney, renal glomerulosclerosis, organ hypertrophy, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome, thrombotic disorders, stroke, cerebral vasospasm, cerebral ischemia, pain, e.g. neuropathic pain, neuronal degeneration, spinal cord injury, Alzheimer's disease, premature birth, erectile dysfunction, endocrine dysfunctions, arteriosclerosis, prostatic hypertrophy, diabetes and complications of diabetes, metabolic syndrome, blood vessel restenosis, atherosclerosis, inflammation, autoimmune diseases, AIDS, osteopathy such as osteoporosis, infection of digestive tracts with bacteria, sepsis, cancer development and progression, e.g. cancers of the breast, colon, prostate, ovaries, brain and lung and their metastases.

Moreover, such a compound is also useful for curative approaches associated with stem cell or induced pluripotent stem cell treatment, improvement of recognition or for treatment or prevention of depression, epilepsy, fibroid heart, renal papillary necrosis, tubulo-interstitial dysfunction, multiple sclerosis, vessel stenosis for example carotid stenosis or lipid disorders.

[0005] WO 2001/64238 describes isoquinoline-5-sulfonamide derivatives optionally substituted by a $-(CH_2)_{1-6}-O-(CH_2)_{0-6}-$, a $-(CH_2)_{0-6}-S-(CH_2)_{0-6}-$ or a $-(CH_2)_{0-6}$ -linked heterocyclic group useful as neuroprotective agents.

[0006] WO 2004/106325 (Schering AG) describes prodrugs of the Rho-kinase inhibitor fasudil carrying an ether or ester group in the 1-position of the isoquinoline ring.

[0007] WO 2001/039726 generically describes $-O-(C_0-C_{10})$ alkyl-heteroaryl substituted cyclohexyl derivatives useful for the treatment of microbial infections.

JP 10087629 A describes isoquinoline derivatives useful for the treatment of diseases caused by *Helicobacter pylori* such as for example gastritis cancer or ulcer. The isoquinoline derivatives may be substituted by OH in the 1-position and are preferably 5-substituted by $X-[(C_1-C_6)alkylene]_{0-1}-Y$ wherein X may be oxygen and Y may be an aryl or a heterocyclic group.

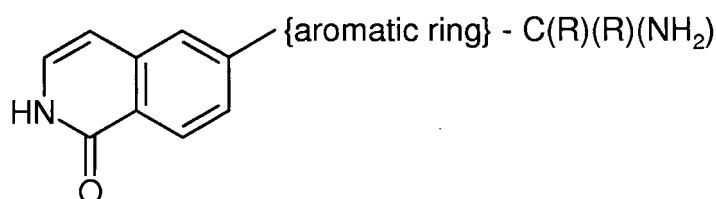
[0008] Hagihara et al. (Bioorg. Med. Chem. 1999, 7, 2647-2666) disclose 6-benzyloxyisoquinoline for the treatment of infections caused by *Helicobacter pylori*.

[0009] US 5,480,883 generically discloses as EGF and/or PDGF receptor inhibitors useful for inhibiting cell proliferation compounds of the formula "Ar I - X - Ar II" wherein X may be $(CHR_1)_m-Z-(CHR_1)_n$, e.g. $Z-CH_2$, wherein Z may be O, R_1 is hydrogen or alkyl, Ar I may be among others an optionally substituted isoquinolone and Ar II may be among others an optionally substituted C_{3-7} monocyclic saturated heterocyclic system.

[0010] WO 2005/030791 (Merck & Co.) generically describes as potassium channel inhibitors for the treatment of cardiac arrhythmias, stroke, congestive heart failure etc. isoquinolone derivatives which are optionally substituted in 6-position by a group $(CR^eR^f)_pOR^{43}$ wherein p may be zero, and R^{43} is e.g. a (C_3-C_{10}) cycloalkyl residue optionally substituted by $NR^{51}R^{52}$, wherein R^{51} and R^{52} may be hydrogen, (C_1-C_6) alkyl etc.; or R^{43} is a group R^{81} defined as a 4-6 membered unsaturated or saturated monocyclic heterocyclic ring with 1, 2, 3 or 4 heteroatoms; and are substituted by a directly bound optionally substituted aryl or heteroaryl ring in the 4-position.

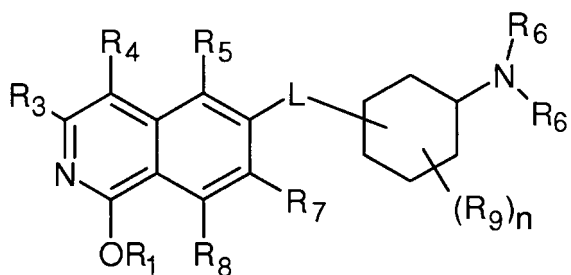
[0011] WO 2005/030130 (Merck & Co.) generically describes as potassium channel inhibitors for the treatment of cardiac arrhythmias, stroke, congestive heart failure etc. isoquinoline derivatives which may be substituted by hydroxy in the 1-position and are optionally substituted in 6-position by a group $(CR^eR^f)_pOR^{43}$ wherein p may be zero, and R^{43} is e.g. a (C_3-C_{10}) cycloalkyl residue optionally substituted by $NR^{51}R^{52}$, wherein R^{51} and R^{52} may be hydrogen, (C_1-C_6) alkyl etc.; or R^{43} is a group R^{81} defined as a 4-6 membered unsaturated or saturated monocyclic heterocyclic ring with 1, 2, 3 or 4 heteroatoms; and are substituted by a directly bound optionally substituted aryl or heteroaryl ring in the 4-position.

[0012] WO2003/053330 (Ube) generically describes isoquinolone derivatives of the formula



as Rho-kinase inhibitors.

[0013] WO 2007/012422 (Sanofi-Aventis) generically describes isoquinoline and isoquinolone derivatives of the formula



as Rho-Kinase inhibitors.

[0014] WO2008/077556 (Sanofi-Aventis) describes further 6-substituted isoquinoline and isoquinolone derivatives as Rho-Kinase inhibitors.

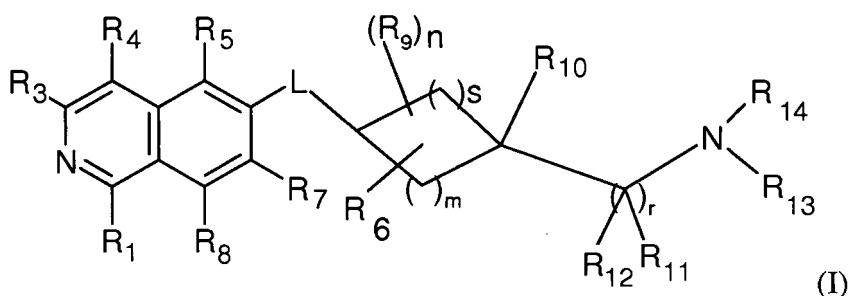
[0015] WO 2008/020081 (Organon) describes 6-substituted isoquinoline-1-one or isoquinoline 1-amine derivatives as Rho-kinase inhibitors.

[0016] Iwakubo et. al. (Bioorganic & Med. Chemistry Vol. 15, No. 1, 15. Nov. 2006, p. 350 - 364) describe a 5-substituted isoquinoline and indazol derived derivatives as Rho-kinase inhibitors.

[0017] In particular selectivity against other kinases has been identified as prerequisite for usage of kinase inhibitors as therapeutic agents. Fasudil for instance, a broadly profiled inhibitor of Rho kinase displays only modest selectivity against several other kinases, for example Protein Kinase A and Protein Kinase G (see for example Tamura et al., Biochimica et Biophysica Acta, Proteins and Proteomics (2005), 1754(1-2), 245-252. Also another inhibitor, Y-27632 only displays a 20-fold selectivity against Protein Kinase G.

Therefore, although several Rho-kinase inhibitors have been described there still remains the need for additional compounds useful in the treatment of Rho-kinase mediated diseases, in particular with improved selectivity.

[0018] An embodiment of the present invention is a compound of the formula (I)



wherein

R_1 is H, OH or NH_2 ;

R_3 is H, halogen, CN, (C_1-C_6) alkyl, OH, NH_2 , or NHR' ;

R_4 is H, halogen, hydroxy, CN, (C_1-C_6) alkyl, R' , or (C_1-C_6) alkylene- R' ;

R_5 is H, halogen, CN, (C_1-C_6) alkyl, or R' ;

R_7 is H, halogen, CN, (C_1-C_6) alkyl, O- (C_1-C_6) alkyl, R' , or SO_2-NH_2 ;

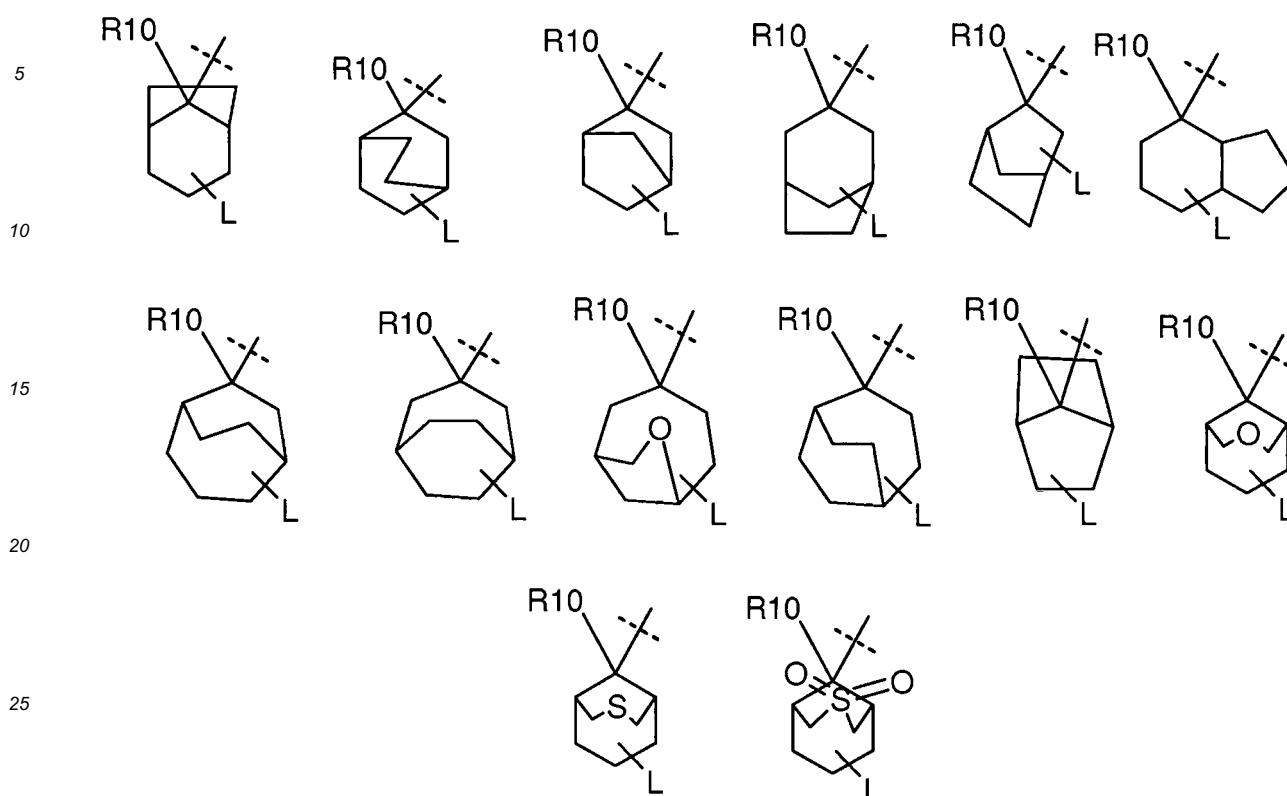
R_8 is H, halogen or (C_1-C_6) alkyl;

R_9 is OH, halogen, (C_1-C_6) alkyl, $C(O)OH$, $C(O)NH_2$, or $O-CH_3$, wherein (C_1-C_6) alkyl is unsubstituted or substituted;

R_6 is absent

or is one (C_1-C_4) alkylene bond to the cycloalkyl ring, in which the (C_1-C_4) alkylene forms a second bond to a different

carbon atom of the cycloalkyl ring to form a bicyclic ring system of formula,

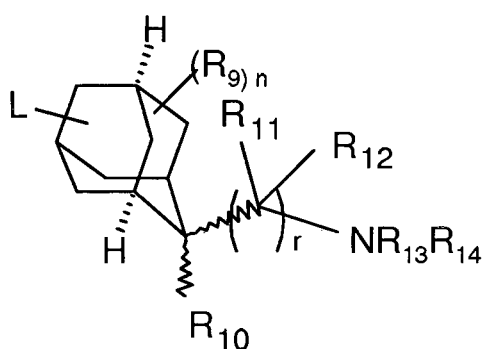


or, if m and s are 2, m is 3 and s is 1, or m is 4 and s is 0,

R_6 is $\text{CH}_2\text{-CH-(CH}_2)_2$ which is bound with one CH_2 to the cycloalkyl ring and the two other CH_2 are bound to different carbon atoms of the cycloalkyl ring;

and, if m is 3 and s is 3,

R_6 are two methylene groups bound to different carbon atoms of the cycloalkyl ring, wherein the methylene groups or the $\text{CH}_2\text{-CH-(CH}_2)_2$ group are bound to carbon atoms of the cycloalkyl ring such that they form an adamantane system of the formula



wherein L can be bound to any secondary or tertiary carbon atom and

wherein the bicyclic ring system or adamantane system is unsubstituted or optionally substituted by R_9 ;

R_{10} is

H, phenyl, O-phenyl, or $(\text{C}_5\text{-C}_6)$ heteroaryl,

wherein phenyl or $(\text{C}_5\text{-C}_6)$ heteroaryl is unsubstituted or substituted;

R_{11} is

H,
 (C₁-C₆)alkyl,
 (C₁-C₆)alkylene-R',
 (C₃-C₈)cycloalkyl,
 (C₅-C₁₀)heteroaryl,
 (C₃-C₈)heterocycloalkyl,
 (C₆-C₁₀)aryl;
 or R₁₁ and R₁₂ together with carbon atom to which they are attached form a (C₃-C₈)cycloalkyl or a (C₃-C₈)-hetero-
 cycloalkyl ring;

R₁₂ is
 (C₁-C₆)alkyl,
 (C₃-C₈)cycloalkyl,
 (C₅-C₁₀)heteroaryl,
 (C₃-C₈)heterocycloalkyl, or
 (C₆-C₁₀)aryl;
 or R₁₂ is H, provided that r = 2 and the other R₁₂ is not H;
 or R₁₁ and R₁₂ together with carbon atom to which they are attached form a (C₃-C₈)cycloalkyl or a (C₃-C₈)-hetero-
 cycloalkyl ring;

R₁₃ and R₁₄ are independently of each other

H,
 R',
 (C₁-C₆)alkyl,
 (C₁-C₆)alkylene-R',
 (C₁-C₆)alkylene-O-(C₁-C₆)alkyl,
 (C₁-C₆)alkylene-O-R',
 C(O)(C₁-C₆)alkyl,
 C(O)R', or
 C(O)(C₁-C₆)alkylene-R'
 C(O)N[(C₁-C₆)alkyl]₂,
 wherein R', (C₁-C₆)alkyl, or (C₁-C₆)alkylene are unsubstituted or substituted, or

R₁₃ and R₁₄, together with the N-atom to which they are attached, form a unsubstituted or substituted (C₃-C₈)
 heterocycloalkyl ring.

n is 0, 1, 2, 3 or 4;

m is 1, 2, 3 or 4;

s is 0, 1, 2, or 3;

r is 1 or 2;

L is O, S, S or NH;

R' is
 (C₃-C₈)cycloalkyl,
 (C₅-C₁₀)heteroaryl,
 (C₃-C₈)heterocycloalkyl,
 (C₆-C₁₀)aryl;

wherein in residues R₃ to R₁₄ alkyl or alkylene is unsubstituted or optionally substituted one or more times by OH, OCH₃,
 C(O)OH, C(O)OCH₃, NH₂, NHCH₃,
 N(CH₃)₂, C(O)NH₂, C(O)NHCH₃ or C(O)N(CH₃)₂;
 wherein in residues R₃ to R₁₄ cycloalkyl or heterocycloalkyl is unsubstituted or optionally substituted one or more times
 by (C₁-C₆)alkyl, halogen, OH, OCH₃, C(O)OH, C(O)OCH₃, NH₂, NHCH₃, N(CH₃)₂, C(O)NH₂, C(O)NHCH₃ or
 C(O)N(CH₃)₂;

wherein in residues R₃ to R₁₄ alkyl or alkylene is unsubstituted or optionally substituted one or more times by halogen; wherein in residues R₃ to R₁₄ (C₆-C₁₀)aryl and (C₅-C₁₀)heteroaryl are unsubstituted or optionally substituted one or more times by a group independently selected from halogen, OH, NO₂, N₃, CN, C(O)-(C₁-C₆)alkyl, C(O)-(C₆-C₁₀)aryl, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂, (C₃-C₈)cycloalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkylene-NH(C₁-C₆)alkyl, (C₁-C₆)alkylene-N[(C₁-C₆)alkyl]₂, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, O-(C₁-C₆)alkyl, O-C(O)-(C₁-C₆)alkyl, PO₃H₂, SO₃H, SO₂-NH₂, SO₂NH(C₁-C₆)alkyl, SO₂N[(C₁-C₆)alkyl]₂, S-(C₁-C₆)alkyl, SO-(C₁-C₆)alkyl, SO₂-(C₁-C₆)alkyl, SO₂-N=CH-N[(C₁-C₆)alkyl]₂, SF₅, C(NH)(NH₂), NH₂, NH-(C₁-C₆)alkyl, N[(C₁-C₆)alkyl]₂, NH-C(O)-(C₁-C₆)alkyl, NH-C(O)O-(C₁-C₆)alkyl, NH-SO₂-(C₁-C₆)alkyl, NH-SO₂-(C₆-C₁₀)aryl, NH-SO₂-(C₅-C₁₀)heteroaryl, NH-SO₂-(C₃-C₈)heterocycloalkyl, N(C₁-C₆)alkyl-C(O)-(C₁-C₆)alkyl, N(C₁-C₆)alkyl-C(O)O-(C₁-C₆)alkyl, N(C₁-C₆)alkyl-C(O)-NH-(C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₁-C₆)alkylene-(C₆-C₁₀)aryl, O-(C₆-C₁₀)aryl, O-(C₁-C₆)alkylene-(C₆-C₁₀)aryl, (C₅-C₁₀)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₁-C₆)alkylene-(C₅-C₁₀)heteroaryl, (C₁-C₆)alkylene-(C₃-C₈)heterocycloalkyl, O-(C₁-C₆)alkylene-(C₅-C₁₀)heteroaryl, O-(C₁-C₆)alkylene-(C₃-C₈)heterocycloalkyl,

wherein said (C₆-C₁₀)aryl, (C₅-C₁₀)heteroaryl, (C₃-C₈)heterocycloalkyl or (C₃-C₈)cycloalkyl may be substituted one to three times by a group independently selected from halogen, OH, NO₂, CN, O-(C₁-C₆)alkyl, (C₁-C₆)alkyl, NH₂, NH(C₁-C₆)alkyl, N[(C₁-C₆)alkyl]₂, SO₂CH₃, COOH, C(O)O-(C₁-C₆)alkyl, CONH₂, (C₁-C₆)alkylene-O-(C₁-C₆)alkyl, (C₁-C₆)alkylene-O-(C₆-C₁₀)aryl, or O-(C₁-C₆)alkylene-(C₆-C₁₀)aryl; or wherein (C₆-C₁₀)aryl is vicinally substituted by a O-(C₁-C₄)alkylene-O group whereby a 5-8-membered ring is formed together with the carbon atoms the oxygen atoms are attached to; and

wherein aryl substituents of (C₆-C₁₀)aryl, (C₅-C₁₀)heteroaryl, (C₃-C₈)heterocycloalkyl or (C₃-C₈)cycloalkyl groups may not be further substituted by an aryl, heteroaryl, heterocycloalkyl, or (C₃-C₈)cycloalkyl containing group; their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts thereof.

[0019] In another embodiment the present invention also relates to a compound of formula (I) and/or its pharmaceutically acceptable salt for use as a medicament. It also relates to the use of at least one compound of formula (I) and/or a pharmaceutically acceptable salt thereof for the treatment and/or prevention of Rho-Kinase mediated diseases such as hypertension, pulmonary hypertension, ocular hypertension, retinopathy, glaucoma, peripheral circulatory disorder, peripheral arterial occlusive disease (PAOD), coronary heart disease, angina pectoris, heart hypertrophy, heart failure, ischemic diseases, ischemic organ failure (end organ damage), fibroid lung, fibroid liver, liver failure, nephropathy, renal failure, fibroid kidney, renal glomerulosclerosis, organ hypertrophy, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome, thrombotic disorders, stroke, cerebral vasospasm, cerebral ischemia, pain, neuronal degeneration, spinal cord injury, Alzheimer's disease, premature birth, erectile dysfunction, endocrine dysfunctions, arteriosclerosis, prostatic hypertrophy, diabetes and complications of diabetes, metabolic syndrome, blood vessel restenosis, atherosclerosis, inflammation, autoimmune diseases, AIDS, osteopathy, infection of digestive tracts with bacteria, sepsis or cancer development and progression. The invention further relates to a medicament comprising an effective amount of at least one compound of formula (I) and/or a pharmacologically acceptable salt thereof. Another object of the present invention is a method of producing a compound of formula (I).

[0020] The term alkyl as used in (C₁-C₂)alkyl, (C₁-C₄)alkyl, or (C₁-C₆)alkyl and the corresponding alkylene substituents are understood as a hydrocarbon residue which can be linear, i.e. straight-chain, or branched and has 1, 2, 3, 4, 5, or 6 carbon atoms, respectively. This also applies if an alkyl group occurs as a substituent on another group, for example in an alkoxy group (O-alkyl), S-alkyl or a -O(C₁-C₆)alkylene-O-, an alkoxycarbonyl group or an arylalkyl group. Examples of alkyl groups are methyl, ethyl, propyl, butyl, pentyl or hexyl, the n-isomers of all these groups, isopropyl, isobutyl, 1-methylbutyl, isopentyl, neopentyl, 2,2-dimethylbutyl, 2-methylpentyl, 3-methylpentyl, isohexyl, sec-butyl, tert-butyl or tert-pentyl. Alkyl or alkylene groups may optionally be halogenated once or more, e.g. alkyl groups may be fluorinated, e.g. perfluorinated. Examples of halogenated alkyl groups are CH₂F, CHF₂, CF₃ and CH₂CF₃, OCF₃, SCF₃, or -O-(CF₂)₂-O-.

[0021] The term (C₂-C₆)-alkenyl means a hydrocarbon residue whose carbon chain is straight-chain or branched and comprises 2 to 6 carbon atoms and has, depending on the chain length, 1, 2 or 3 double bonds, for example, vinyl, 1-propenyl, 2-propenyl (= allyl), 2-butenyl, 3-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 5-hexenyl or 1,3-pentadienyl. The double bond may where possible have the E or Z orientation. The double bonds may be both internal and terminal.

[0022] (C₂-C₆)-alkynyl groups are hydrocarbon residue whose carbon chain is straight-chain or branched and comprises 2 to 6 carbon atoms and have, depending on the chain length, 1 or 2 triple bonds, for example, ethynyl, 1-propynyl, 2-propynyl (= propargyl) or 2-butyne. The triple bonds may be both internal and terminal.

[0023] Halogen means fluoro (F), chloro (Cl), bromo (Br) or iodo (I).

[0024] The term (C₁-C₈)heteroalkyl or the corresponding (C₁-C₈)heteroalkylene substituents are understood as (C₁-C₈)alkyl or (C₁-C₈)alkylene groups wherein at least one carbon atom, preferably one or two carbon atoms, more preferred one carbon atom, is replaced by a group selected from O, NH, or S and wherein the nitrogen and sulfur atoms may optionally be oxidized. The heteroatom may be placed at any position of the alkyl or alkylene group. Examples of (C₁-C₈)heteroalkyl groups include -CH₂-O-CH₃, -CH₂-CH₂-O-CH₂-CH₃, -CH₂-NH-CH₂-CH₃, -CH₂-N(CH₂-CH₃)₂

-CH₂-CH₂-CH₂-O-CH₃, -CH₂-CH₂-CH₂-S-CH₃, -CH₂-O-CH(CH₃)₂, -CH₂-O-CH₂-CH₂-O-CH₃ or O-CH₂-CH₃.

[0025] (C₃-C₈)cycloalkyl groups are cyclic alkyl groups containing 3, 4, 5, 6, 7 or 8 ring carbon atoms like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cyclooctyl, which can also be substituted and/or contain 1 or 2 double bonds (unsaturated cycloalkyl groups) like, for example, cyclopentenyl or cyclohexenyl, which can be bonded via any carbon atom.

[0026] A (C₆-C₁₀)aryl group means an aromatic ring or a ring system which comprises two aromatic rings which are fused or otherwise linked or which comprises two fused aromatic rings wherein one ring is saturated or partly saturated, i.e. contains at least one C-C single bond, for example a phenyl, naphthyl, biphenyl, tetrahydronaphthyl, alpha- or beta-tetralon-, indanyl- or indan-1-on-yl group. A preferred (C₆-C₁₀)aryl group is phenyl.

[0027] (C₃-C₈)heterocycloalkyl group means a saturated (contains no double bonds) monocyclic carbon ring system containing 3, 4, 5, 6, 7 or 8 ring atoms in which one or more carbon atoms can be replaced by one or more heteroatoms such as, for example 1, 2 or 3 nitrogen atoms, 1 or 2 oxygen atoms, 1 or 2 sulfur atoms or combinations of different hetero atoms. The heterocycloalkyl residues can be bound at any positions, for example on the 1-position, 2-position, 3-position, 4-position, 5-position, 6-position, 7-position or 8-position. Also included are the corresponding N-oxides, sulfoxides or sulfones of these compounds.

[0028] Examples of (C₃-C₈)heterocycloalkyl groups are oxiranyl, oxetanyl, aziridinyl, tetrahydrofuranyl, tetrahydropyranyl, dioxolanyl, for example 1,3-dioxolanyl, dioxanyl, for example 1,4-dioxanyl, piperidinyl, pyrrolidinyl, imidazolidinyl, triazolidinyl, hexahydropyrimidinyl, piperazinyl, triazinanyl, for example, 1,3,5-triazinanyl, 1,2,3-triazinanyl or 1,2,4-triazinanyl, tetrahydrothiophenyl, tetrahydro-thiopyranyl, dithiolanyl, for example 1,3-dithiolanyl, dithianyl, thiazolidinyl, oxazolidinyl, oxathiolanyl, for example 1,3-oxathiolanyl, morpholinyl or thiomorpholinyl, diazepanyl, for example 1,4-diazepanyl.

A preferred (C₃-C₈)heterocycloalkyl group is morpholinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxetanyl or tetrahydropyranyl.

[0029] (C₅-C₁₀)heteroaryl means a mono- or bicyclic ring system in which one or more carbon atoms can be replaced by one or more heteroatoms such as, for example 1, 2, 3 or 4 nitrogen atoms, 1 or 2 oxygen atoms, 1 or 2 sulfur atoms or combinations of different hetero atoms. The heteroaryl residues can be bound at any position, for example on the 1-position, 2-position, 3-position, 4-position, 5-position, 6-position, 7-position or 8-position. (C₅-C₁₀)heteroaryl groups may be an (1) aromatic monocyclic or bicyclic ring system or (2) a bicyclic ring system wherein one ring is aromatic and the second ring is at least partially saturated.

Also included are the corresponding N-oxides, sulfoxides or sulfones of these compounds.

[0030] Suitable (C₅-C₁₀)heteroaryl groups are benzimidazolyl, benzofuryl, benzothieryl, azaindolyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benzisoxazolyl, benzisothiazolyl, carbolinyl, cinnolyl, chromanyl, chromenyl, naphthyridinyl, phthalazinyl, pyridoimidazolyl, pteridinyl, purynyl, quinazolinyl, quinoxalinyl, quinolyl, isoquinolyl, tetrahydroisoquinolyl, tetrahydroquinolyl, indolyl, indolizyl, indolyl, furyl, furazanyl, thienyl, imidazolyl, imidazolyl, 1 H-indazolyl, pyrazolyl, oxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolinyl, pyrrolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl.

Pyridyl stands both for 2-, 3- and 4-pyridyl. Thienyl stands both for 2- and 3-thienyl. Furyl stands both for 2- and 3-furyl. Also included are the corresponding N-oxides of these compounds, for example, 1-oxy-2-, 3- or 4-pyridyl.

[0031] Substitutions in (C₅-C₁₀)heteroaryl residues can occur on free carbon atoms or on nitrogen atoms.

[0032] Preferred examples of (C₅-C₁₀)heteroaryl residues are benzofuryl, quinolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, triazolyl, oxadiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl and tetrazolyl.

[0033] A preferred (C₅-C₁₀)heteroaryl is a (C₅-C₆)heteroaryl group. Preferred (C₅-C₆)heteroaryl residues are furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, triazolyl, oxadiazolyl, pyrazinyl, pyrimidinyl, and pyridazinyl. Preferred examples of (C₅-C₆)heteroaryl residues are 2- or 3-thienyl, 2- or 3-furyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-oxadiazol-2- or -5-yl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, 3- or 4-pyridazinyl, or pyrazinyl.

[0034] In residues R₃ to R₁₄ (C₆-C₁₀)aryl and (C₅-C₁₀)heteroaryl residues are unsubstituted or, if not specified otherwise, optionally substituted one or more times, preferably one to three times, more preferably once, by a group independently selected from halogen, OH, NO₂, N₃, CN, C(O)-(C₁-C₆)alkyl, C(O)-(C₆-C₁₀)aryl, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂, (C₃-C₈)cycloalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkylene-NH(C₁-C₆)alkyl, (C₁-C₆)alkylene-N[(C₁-C₆)alkyl]₂, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, O-(C₁-C₆)alkyl, O-C(O)-(C₁-C₆)alkyl, PO₃H₂, SO₃H, SO₂-NH₂, SO₂NH(C₁-C₆)alkyl, SO₂N[(C₁-C₆)alkyl]₂, S-(C₁-C₆)alkyl, SO-(C₁-C₆)alkyl, SO₂-(C₁-C₆)alkyl, SO₂-N=CH-N[(C₁-C₆)alkyl]₂, SF₅, C(NH)(NH₂), NH₂, NH-(C₁-C₆)alkyl, N[(C₁-C₆)alkyl]₂, NH-C(O)-(C₁-C₆)alkyl, NH-C(O)O-(C₁-C₆)alkyl, NH-SO₂-(C₁-C₆)alkyl, NH-SO₂-(C₆-C₁₀)aryl, NH-SO₂-(C₅-C₁₀)heteroaryl, NH-SO₂-(C₃-C₈)heterocycloalkyl, N(C₁-C₆)alkyl-C(O)-(C₁-C₆)alkyl, N(C₁-C₆)alkyl-C(O)O-(C₁-C₆)alkyl, N(C₁-C₆)alkyl-C(O)-NH-(C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₁-C₆)alkylene-(C₆-C₁₀)aryl, O-(C₆-C₁₀)aryl, O-(C₁-C₆)alkylene-(C₆-C₁₀)aryl, (C₅-C₁₀)heteroaryl,

(C₃-C₈)heterocycloalkyl, (C₁-C₆)alkylene-(C₅-C₁₀)heteroaryl, (C₁-C₆)alkylene-(C₃-C₈)heterocycloalkyl, O-(C₁-C₆)alkylene-(C₅-C₁₀)heteroaryl, O-(C₁-C₆)alkylene-(C₃-C₈)heterocycloalkyl, wherein said (C₆-C₁₀)aryl, (C₅-C₁₀)heteroaryl, (C₃-C₈)heterocycloalkyl or (C₃-C₈)cycloalkyl may be substituted one to three times by a group independently selected from halogen, OH, NO₂, CN, O-(C₁-C₆)alkyl, (C₁-C₆)alkyl, NH₂, NH(C₁-C₆)alkyl, N[(C₁-C₆)alkyl]₂, SO₂CH₃, COOH, C(O)O-(C₁-C₆)alkyl, CONH₂, (C₁-C₆)alkylene-O-(C₁-C₆)alkyl, (C₁-C₆)alkylene-O-(C₆-C₁₀)aryl, or O-(C₁-C₆)alkylene-(C₆-C₁₀)aryl; or

wherein (C₆-C₁₀)aryl is vicinally substituted by a O-(C₁-C₄)alkylene-O group whereby a 5-8-membered ring is formed together with the carbon atoms the oxygen atoms are attached to; and

wherein aryl substituents of (C₆-C₁₀)aryl, (C₅-C₁₀)heteroaryl, (C₃-C₈)heterocycloalkyl or (C₃-C₈)cycloalkyl groups may not be further substituted by an aryl, heteroaryl, heterocycloalkyl, or (C₃-C₈)cycloalkyl containing group.

[0035] Preferred substituents for (C₆-C₁₀)aryl and (C₅-C₁₀)heteroaryl groups are OH, (C₁-C₄)alkyl, O-(C₁-C₄)alkyl, O-phenyl, phenyl, C(O)O-(C₁-C₆)alkyl, C(O)OH, C(O)-(C₁-C₄)alkyl, halogen, NO₂, SO₂NH₂, CN, SO₂-(C₁-C₄)alkyl, SO₂-N=CH-N[(C₁-C₆)alkyl]₂, NH-SO₂-(C₁-C₄)alkyl, NH₂, NH-C(O)-(C₁-C₄)alkyl, (C₃-C₈)cycloalkyl, (C₁-C₄)alkyl-OH, C(O)N[(C₁-C₄)alkyl]₂, C(O)NH(C₁-C₆)alkyl, C(O)NH₂, N[(C₁-C₄)alkyl]₂, (C₁-C₄)alkylene-N[(C₁-C₄)alkyl]₂, (C₁-C₄)alkylene-O-(C₁-C₄)alkyl, (C₅-C₆)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₁-C₄)alkylene-(C₆-C₁₀)aryl, wherein the (C₆-C₁₀)aryl may be further substituted one to three times, preferably once, by halogen, (C₁-C₄)alkyl, O-(C₁-C₄)alkyl, (C₁-C₄)alkylene-O-(C₁-C₆)alkyl, (C₆-C₁₀)aryl, O-(C₁-C₆)alkylene-(C₆-C₁₀)aryl, or may be vicinally substituted by a O-(C₁-C₄)alkylene-O group whereby a 5-8-membered ring is formed together with the carbon atoms the oxygen atoms are attached to.

[0036] More preferred substituents for (C₆-C₁₀)aryl and (C₅-C₁₀)heteroaryl are OH, halogen, CN, phenyl, O-phenyl, NH-C(O)-(C₁-C₄)alkyl, C(O)-(C₁-C₄)alkyl, C(O)-O-(C₁-C₄)alkyl, (C₁-C₄)alkyl, O-(C₁-C₄)alkyl, CONH₂, SO₂-NH₂, SO₂-(C₁-C₄)alkyl or SO₂-N=CH-N[(C₁-C₄)alkyl]₂, (C₁-C₄)alkylene-phenyl, (C₁-C₄)alkylene-O-(C₁-C₄)alkyl or (C₅-C₆)heteroaryl, wherein the phenyl is unsubstituted or optionally substituted one to three times, preferably once, by OH, halogen, (C₁-C₄)alkyl or O-(C₁-C₄)alkyl. Even more preferred substituents for (C₆-C₁₀)aryl and (C₅-C₁₀)heteroaryl are OH, halogen, CN, phenyl, O-phenyl, NH-C(O)-(C₁-C₄)alkyl especially NH-C(O)-CH₃, C(O)-(C₁-C₄)alkyl especially C(O)-CH₃, C(O)-O-(C₁-C₄)alkyl especially C(O)-OCH₃, (C₁-C₄)alkyl especially CH₃ or CF₃, O-(C₁-C₄)alkyl especially O-CH₃, CONH₂, SO₂-NH₂, SO₂-(C₁-C₄)alkyl especially SO₂-CH₃ or SO₂-CF₃; or SO₂-N=CH-N[(C₁-C₄)alkyl]₂ especially SO₂-N=CH-N[(CH₃)₂],

wherein the phenyl is unsubstituted or optionally substituted one to three times, preferably once, by OH, halogen, (C₁-C₄)alkyl or O-(C₁-C₄)alkyl.

[0037] More especially preferred substituents for (C₆-C₁₀)aryl and (C₅-C₁₀)heteroaryl groups are OH, CN, (C₁-C₄)alkyl especially CH₃ or CF₃, O-(C₁-C₄)alkyl especially O-CH₃, halogen or phenyl, wherein the phenyl may be further substituted one to three times, preferably once, by OH, halogen, (C₁-C₄)alkyl especially CH₃ or CF₃, or O-(C₁-C₄)alkyl especially O-CH₃.

[0038] Most preferred substituents for (C₆-C₁₀)aryl and (C₅-C₁₀)heteroaryl groups are OH, CN, halogen, (C₁-C₄)alkyl especially CH₃ or CF₃, O-(C₁-C₄)alkyl especially O-CH₃, or halogen.

[0039] In monosubstituted phenyl groups the substituent can be located in the 2-position, the 3-position or the 4-position, with the 3-position and the 4-position being preferred. If a phenyl group carries two substituents, they can be located in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In phenyl groups carrying three substituents the substituents can be located in 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position, or 3,4,5-position.

[0040] The above statements relating to phenyl groups correspondingly apply to divalent groups derived from phenyl groups, i.e. phenylene which can be unsubstituted or substituted 1,2-phenylene, 1,3-phenylene or 1,4-phenylene. The above statements also correspondingly apply to the aryl subgroup in arylalkylene groups. Examples of arylalkylene groups which can also be unsubstituted or substituted in the aryl subgroup as well as in the alkylene subgroup, are benzyl, 1-phenylethylene, 2-phenylethylene, 3-phenylpropylene, 4-phenylbutylene, 1-methyl-3-phenyl-propylene.

[0041] In residues R₃ to R₁₄ an alkyl or alkylene is unsubstituted or, if not specified otherwise, optionally substituted one or more times by halogen. If substituted, alkyl or alkylene is preferably substituted one to three times by halogen selected from chloro or bromo but may be substituted by fluoro once or more, e.g. being perfluorinated. Preferably halogen is fluoro. Preferably alkylene is not halogenated. More preferred an alkyl or alkylene is not halogenated.

[0042] In residues R₃ to R₁₄ alkyl or alkylene is unsubstituted or, if not specified otherwise, optionally substituted one or more times by a group selected independently from OH, OCH₃, C(O)OH, C(O)OCH₃, NH₂, NHCH₃, N(CH₃)₂, C(O)NH₂, C(O)NHCH₃ or C(O)N(CH₃)₂. If substituted, the number of substituents is preferably between 1, 2, 3 or 4, more preferably 1 or 2 with 1 being even more preferred. Preferably an alkylene is not substituted by one of these groups. More preferably an alkyl or alkylene is not substituted by one of these groups. Preferably alkyl or alkylene in R₃, R₄, R₅, R₇ and R₈ are not substituted. In a further embodiment alkyl or alkylene in R₄ to R₁₅ is not substituted by one of these groups.

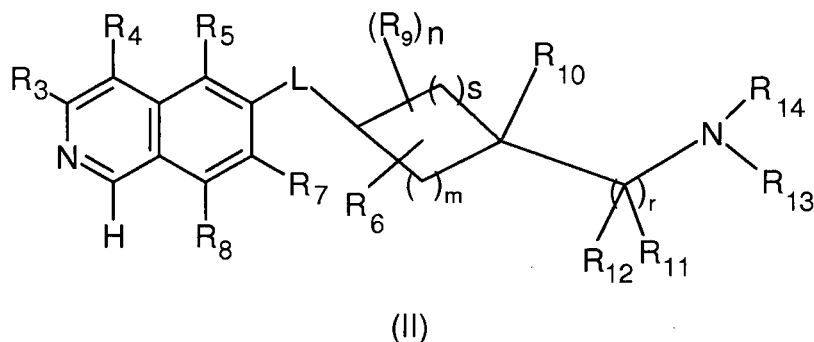
[0043] In residues R₃ to R₁₄ cycloalkyl or heterocycloalkyl is unsubstituted or, if not specified otherwise, optionally substituted one or more times by (C₁-C₆)alkyl, halogen, OH, OCH₃, C(O)OH, C(O)OCH₃, NH₂, NHCH₃, N(CH₃)₂,

C(O)NH₂, C(O)NHCH₃ or C(O)N(CH₃)₂. If substituted, the number of substituents is preferably between 1, 2, 3 or 4, more preferably 1 or 2 with 1 being even more preferred. Preferably cycloalkyl or heterocycloalkyl in R₃ to R₉ are not substituted. In a further embodiment cycloalkyl or heterocycloalkyl in R₃ to R₁₅ are not substituted. In a preferred embodiment a heterocycloalkyl is not substituted. In another embodiment cycloalkyl is not substituted.

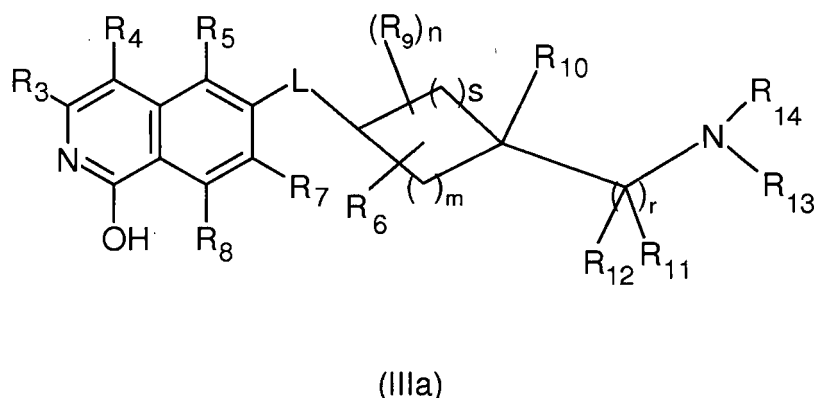
[0044] The general and preferred substituents of (C₆-C₁₀)aryl, (C₅-C₁₀)heteroaryl, (C₃-C₈)heterocycloalkyl and (C₃-C₈)cycloalkyl groups as defined before may be combined with the general and preferred definitions of R₁, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, n, s, m, r, p and L as described in the following embodiments of a compound of formula (I).

[0045] The following embodiments of a compound of formula (I) do further characterize and are part of the present invention.

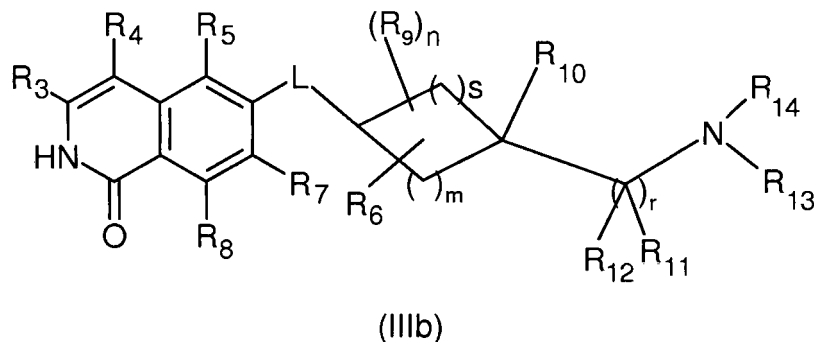
In one embodiment of a compound of formula (I) R₁ is H and the compound is characterized by the formula (II)



[0046] In another embodiment of the present invention R₁ is OH and the compound is characterized by the formula (IIIa)

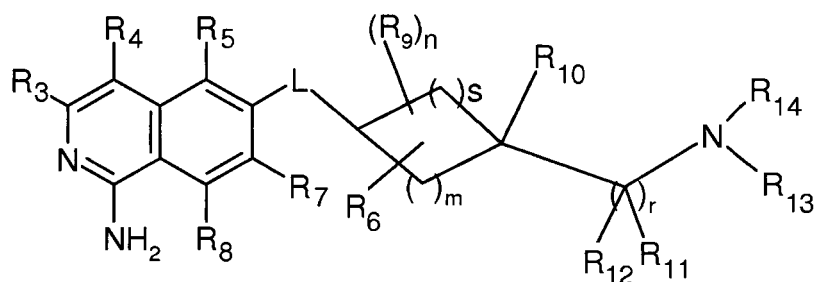


[0047] The isoquinoline derivative of formula (I), wherein R₁ is OH, includes the corresponding tautomeric 1-isoquinolone derivative which is characterized by the formula (IIIb)



[0048] This tautomeric form is also an embodiment of the present invention.

[0049] In a further embodiment R₁ is NH₂ and the compound is characterized by the formula (IV)

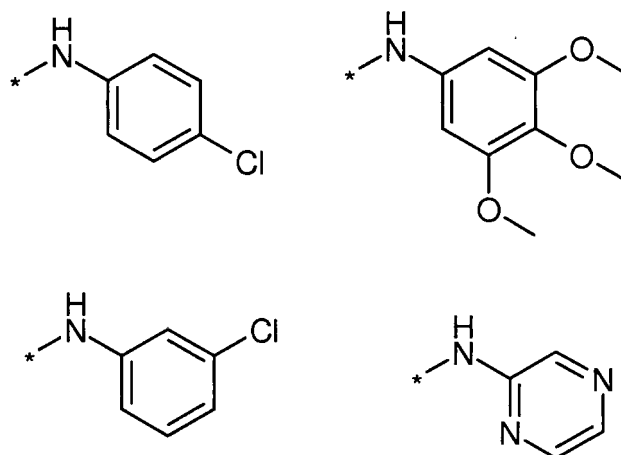


(IV)

[0050] The following further embodiments equally refer to the compounds of formula (I), (II), (IIIa), (IIIb) and (IV).

[0051] In a preferred embodiment R_1 is H or OH; more preferably R_1 is OH.

[0052] In one embodiment R_3 is preferably H, halogen, (C_1-C_6) alkyl, or NHR' . In another more preferred embodiment R_3 is H, halogen, unsubstituted or substituted $NH-(C_5-C_6)$ heteroaryl, unsubstituted or substituted $NH-(C_3-C_8)$ heterocycloalkyl or unsubstituted or substituted NH -phenyl. In a even more preferred embodiment R_3 is unsubstituted or substituted $NH-(C_5-C_6)$ heteroaryl containing one or more N atoms, or unsubstituted or substituted NH -phenyl. In a most preferred embodiment R_3 is H. Examples of NHR' substituents in R_3 are



[0053] The asterisk (*) denotes where the bond is connected to the C-atom of the ring.

[0054] In a preferred embodiment R_4 is H, halogen, (C_1-C_6) alkyl, or (C_1-C_2) -alkylene-phenyl. In a more preferred embodiment R_4 is H, halogen or unsubstituted or substituted (C_1-C_4) alkyl or (C_1-C_2) -alkylene-phenyl, preferably unsubstituted (C_1-C_4) alkyl or (C_1-C_2) -alkylene-phenyl. Even more preferred R_4 is H or halogen, with H being most preferred.

[0055] In a preferred embodiment R_5 is H, CN, halogen, unsubstituted or substituted (C_1-C_6) alkyl, unsubstituted or substituted (C_6-C_{10}) aryl, substituted or unsubstituted (C_3-C_8) cycloalkyl or unsubstituted or substituted (C_5-C_{10}) heteroaryl. (C_6-C_{10}) aryl is preferably phenyl. Examples of R_5 are hydrogen, fluoro, chloro, bromo, iodo, methyl, ethyl, phenyl, thienyl or pyridyl, nitrile, (p-methoxy)-phenyl, N-aniline, cyclopropyl, tetrazol, 4-methoxy-aniline. In a more preferred embodiment (C_1-C_6) alkyl, (C_6-C_{10}) aryl, (C_3-C_8) cycloalkyl or (C_5-C_{10}) heteroaryl are unsubstituted. In an even more preferred embodiment R_5 is H, halogen, methyl, ethyl, phenyl, thienyl, or pyridyl, more specifically H, halogen, methyl, or ethyl. Most preferred R_5 is H.

[0056] In a preferred embodiment R_7 is H, halogen, nitrile, unsubstituted or substituted (C_1-C_6) alkyl, unsubstituted or substituted $O-(C_1-C_6)$ alkyl, or unsubstituted or substituted R' . In a more preferred embodiment R_7 is H, halogen, nitrile, unsubstituted or substituted (C_1-C_4) alkyl, unsubstituted or substituted $O-(C_1-C_4)$ alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted (C_5-C_6) heteroaryl, or unsubstituted or substituted (C_3-C_6) cycloalkyl. Preferably, alkyl, phenyl or (C_5-C_6) heteroaryl are unsubstituted.

In an even more preferred embodiment R_7 is H, fluoro, chloro, bromo, methyl, ethyl, methoxy, phenyl, nitrile, cyclopropyl, or thienyl. More preferably R_7 is H, fluoro, chloro, bromo, methyl or methoxy, in particular H, methyl or chloro. Most preferred R_7 is chloro.

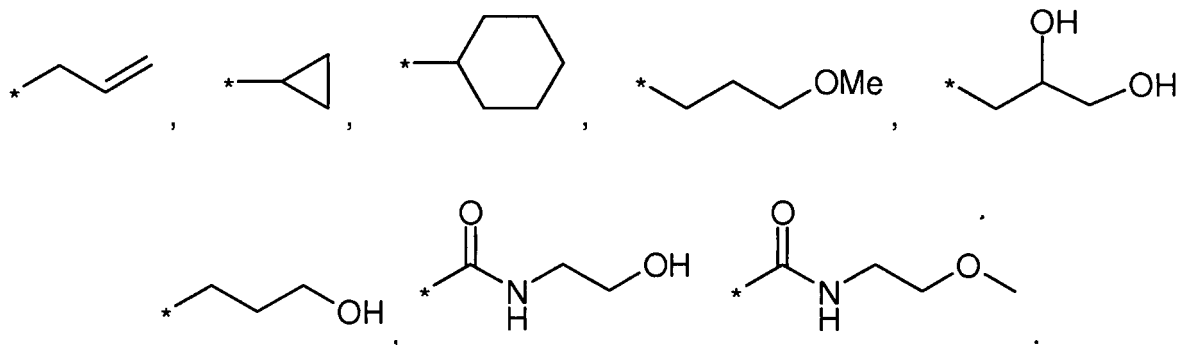
[0057] In a preferred embodiment R_8 is H, Cl, F, methyl or ethyl. In a more preferred embodiment R_8 is H.

[0058] It is described a R_9 residue which is R' , OH, halogen, (C_1-C_6) alkyl, (C_1-C_6) alkylene- R' , (C_2-C_6) alkenyl, (C_1-C_6) alkylene- $C(O)NH-R'$, (C_1-C_6) alkylene- $C(O)NH-(C_1-C_6)$ alkyl, $COOH$, $CONH_2$, $C(O)NH-(C_1-C_6)$ alkyl, $C(O)NHR'$,

C(O)-NH-(C₁-C₆)alkynyl, C(O)-NH(C₁-C₆)alkylene-R', or C(O)N[(C₁-C₆)alkyl]₂; wherein alkyl, alkylene and R' are unsubstituted or substituted. It is described a R₉ residue which is OH, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkylene-R', (C₂-C₆)alkenyl, COOH, CONH₂, C(O)NH-(C₁-C₆)alkyl, C(O)NHR', or C(O)N[(C₁-C₆)alkyl]₂, wherein alkyl, alkylene and R' are unsubstituted or substituted. More preferably R₉ is OH, halogen, (C₁-C₆)alkyl, COOH, CONH₂, or O-CH₃, wherein alkyl is unsubstituted or substituted. In an even more preferred embodiment R₉ is unsubstituted or substituted (C₁-C₆)alkyl, preferably R₉ is unsubstituted (C₁-C₆)alkyl.

[0059] R₉ may be bound to any carbon atom of the ring including the position where the linker group L is bound.

[0060] As examples for these embodiments, R₉ is methyl, ethyl, propyl, isopropyl,



[0061] The asterisk (*) denotes where the bond is connected to the C-atom of the ring.

[0062] It is described a R₁₀ residue which is H,

(C₆-C₁₀)aryl,

O-(C₆-C₁₀)aryl,

O-(C₁-C₂)alkylene-(C₆-C₁₀)aryl, or

(C₅-C₆)heteroaryl,

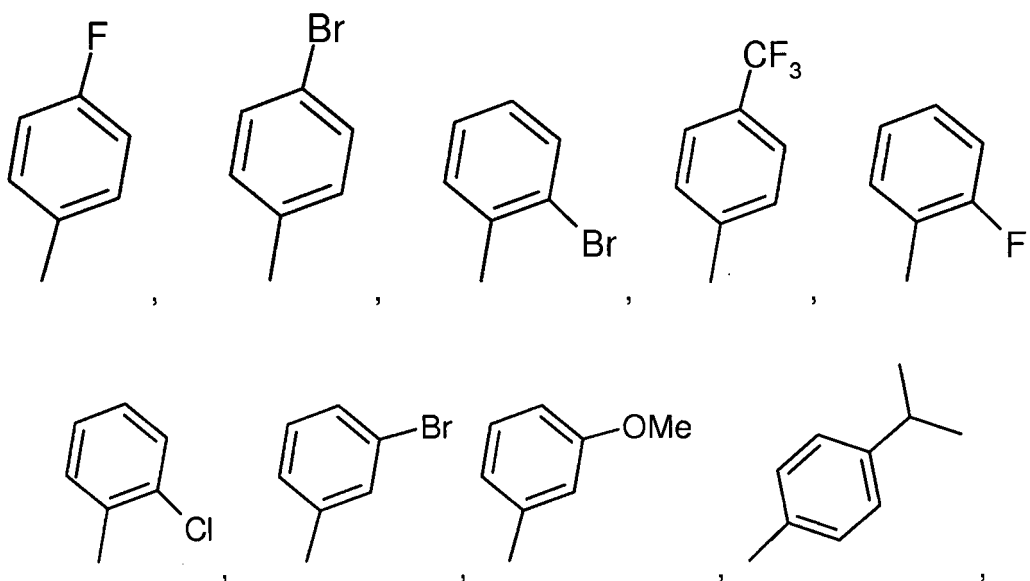
wherein (C₆-C₁₀)aryl or (C₅-C₆)heteroaryl are unsubstituted or substituted. Preferably (C₆-C₁₀)aryl is phenyl.

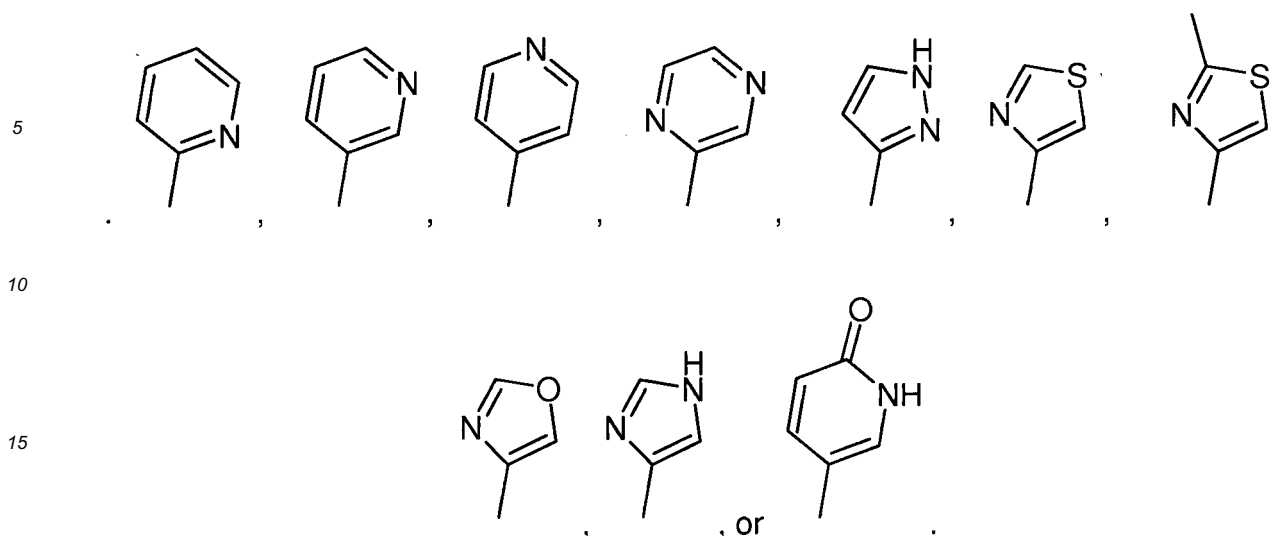
[0063] In a more preferred embodiment R₁₀ is H, phenyl, O-phenyl, or (C₅-C₆)heteroaryl, wherein phenyl or (C₅-C₆)heteroaryl is unsubstituted or substituted.

[0064] In a more preferred embodiment R₁₀ is H or phenyl optionally substituted 1, 2 or 3 times, preferably once, by a group independently selected from C(O)NH₂, OH, CN, halogen, (C₁-C₆)alkyl or O-(C₁-C₆)alkyl, wherein alkyl is unsubstituted or optionally substituted once or more by halogen.

[0065] In an even more preferred embodiment R₁₀ is H or phenyl optionally substituted independently by a group selected from (C₁-C₆)alkyl, F, Cl, Br, OMe or CF₃.

In a most preferred embodiment R₁₀ is H. In still another most preferred embodiment R₁₀ is phenyl. Examples for embodiments of R₁₀ residues are





- [0066]** In a preferred embodiment R_{11} is
H,
 (C_1-C_6) alkyl,
 (C_3-C_8) cycloalkyl, or
 (C_5-C_6) heteroaryl, preferably H or (C_1-C_6) alkyl, wherein (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, or (C_5-C_{10}) heteroaryl are unsubstituted or substituted, preferably unsubstituted.
- [0067]** In a more preferred embodiment R_{11} is H or (C_1-C_6) alkyl, wherein (C_1-C_6) alkyl is unsubstituted or substituted, preferably unsubstituted. Even more preferred R_{11} is H or methyl. Most preferably R_{11} is H.
- [0068]** In a preferred embodiment R_{12} is
 (C_1-C_6) alkyl, wherein optionally one or more hydrogen are substituted by fluoro;
 (C_3-C_8) cycloalkyl,
 (C_5-C_6) heteroaryl, or
 (C_6-C_{10}) aryl, wherein (C_3-C_8) cycloalkyl, (C_5-C_6) heteroaryl and (C_6-C_{10}) aryl are unsubstituted or substituted, preferably (C_3-C_8) cycloalkyl, and (C_5-C_6) heteroaryl are unsubstituted. Preferably (C_6-C_{10}) aryl is phenyl which is unsubstituted or optionally substituted once or twice by a group selected independently of each other from halogen, (C_1-C_4) alkyl or O- (C_1-C_4) alkyl, wherein (C_1-C_4) alkyl may optionally be substituted by fluoro.
- [0069]** In a preferred embodiment R_{12} is methyl, ethyl, propyl, isopropyl, isobutyl, cyclopropyl, trifluoromethyl, thiazolyl or phenyl unsubstituted or substituted by (C_1-C_4) alkyl or halogen. More preferred, R_{12} is methyl, ethyl, propyl, isopropyl, isobutyl, cyclopropyl, or is phenyl optionally substituted by methyl or halogen.
- [0070]** In another embodiment R_{10} is H, R_{11} is H and R_{12} is phenyl optionally substituted 1, 2 or 3 times, preferably once, by a group independently selected from halogen, (C_1-C_6) alkyl or O- (C_1-C_6) alkyl, wherein alkyl is unsubstituted or optionally substituted once or more by halogen.
- [0071]** In another embodiment R_{10} is phenyl optionally substituted 1, 2 or 3 times, preferably once, by a group independently selected from halogen, (C_1-C_6) alkyl or O- (C_1-C_6) alkyl, wherein alkyl is unsubstituted or optionally substituted once or more by halogen; R_{11} is H and R_{12} is unsubstituted (C_3-C_8) cycloalkyl or (C_1-C_6) alkyl, wherein in the alkyl optionally one or more hydrogen are substituted by fluoro; (C_3-C_8) cycloalkyl, or phenyl.
- [0072]** In a further embodiment R_{11} and R_{12} , together with the carbon atom to which they are attached, form a (C_3-C_8) cycloalkyl ring, which is unsubstituted or substituted, preferably unsubstituted. More preferred the ring is cyclopropyl.
- [0073]** In a further embodiment R_{11} and R_{12} , together with the carbon atom to which they are attached, form a (C_3-C_8) heterocycloalkyl ring, which is unsubstituted or substituted. Preferably the formed heterocyclyl group is oxetanyl, morpholinyl, piperidinyl, pyrrolidinyl or piperazinyl. More preferably the heterocyclyl group is morpholinyl or piperazinyl. The formed heterocycloalkyl group is preferably unsubstituted.
- [0074]** In one embodiment of a compound of formula (I) R_{13} and R_{14} are independently of each other
H,
 R' ,
 (C_1-C_6) alkyl,
 (C_1-C_6) alkylene- R' ,
 (C_1-C_6) alkylene-O- (C_1-C_6) alkyl,
 (C_1-C_6) alkylene-O- R' ,

C(O)(C₁-C₆)alkyl,

C(O)R',

C(O)(C₁-C₆)alkylene-R',

C(O)N[(C₁-C₆)alkyl]₂, wherein

5 R', (C₁-C₆)alkyl and (C₁-C₆)alkylene are unsubstituted or substituted.

[0075] In a further embodiment R₁₃ and R₁₄, together with the N-atom to which they are attached, form a (C₃-C₈)-heterocycloalkyl ring, which is unsubstituted or substituted. Preferably, a (C₃-C₈)-heterocycloalkyl is unsubstituted.

[0076] In a preferred embodiment of a compound of formula (I) R₁₃ and R₁₄ are independently of each other H,

10 (C₁-C₆)alkyl,

(C₃-C₈)cycloalkyl,

(C₁-C₄)alkylene-(C₃-C₈)cycloalkyl,

(C₁-C₄)alkylene-(C₅-C₁₀)heteroaryl,

(C₁-C₄)alkylene-(C₃-C₈)heterocycloalkyl,

15 (C₁-C₄)alkylene-(C₆-C₁₀)aryl,

(C₁-C₄)alkylene-O-(C₁-C₆)alkyl,

C(O)(C₁-C₆)alkyl, or

R₁₃ and R₁₄, together with the N-atom to which they are attached, form a (C₃-C₈) heterocycloalkyl group,

20 wherein (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl, (C₁-C₄)alkylene, (C₅-C₁₀)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₆-C₁₀)aryl are unsubstituted or substituted.

[0077] Preferably the formed heterocyclyl group in R₁₃ and R₁₄ is morpholinyl, piperidinyl, pyrrolidinyl or piperazinyl. More preferably the heterocyclyl group is morpholinyl or piperazinyl.

[0078] In a more preferred embodiment of a compound of formula (I)

R₁₃ is H, (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl, or (C₁-C₄)alkylene-(C₃-C₈)cycloalkyl; and R₁₄ is

25 H,

(C₁-C₆)alkyl,

(C₃-C₈)cycloalkyl,

(C₁-C₄)alkylene-(C₃-C₈)cycloalkyl,

(C₁-C₄)alkylene-(C₅-C₁₀)heteroaryl,

30 (C₁-C₄)alkylene-(C₃-C₈)heterocycloalkyl,

(C₁-C₄)alkylene-(C₆-C₁₀)aryl,

(C₁-C₄)alkylene-O-(C₁-C₆)alkyl, or

C(O)(C₁-C₆)alkyl.

wherein (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl, (C₁-C₄)alkylene, (C₃-C₈)heterocycloalkyl, (C₆-C₁₀)aryl are unsubstituted or substituted.

35 **[0079]** In an even more preferred embodiment of a compound of formula (I)

R₁₃ is H or (C₁-C₆)alkyl; and

R₁₄ is

H,

40 (C₁-C₆)alkyl,

(C₃-C₈)cycloalkyl,

(C₁-C₄)alkylene-(C₃-C₈)cycloalkyl,

(C₁-C₄)alkylene-(C₅-C₁₀)heteroaryl,

(C₁-C₄)alkylene-(C₃-C₈)heterocycloalkyl,

45 (C₁-C₄)alkylene-(C₆-C₁₀)aryl, or

(C₁-C₄)alkylene-O-(C₁-C₆)alkyl.

wherein (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl, (C₁-C₄)alkylene, (C₃-C₈)heterocycloalkyl, (C₆-C₁₀)aryl are unsubstituted or substituted.

[0080] More preferably R₁₃ is H, (C₁-C₆)alkyl and

50 R₁₄ is H, (C₁-C₆)alkyl or (C₃-C₈)cycloalkyl, wherein (C₁-C₆)alkyl or (C₃-C₈)cycloalkyl are unsubstituted or substituted, preferably unsubstituted.

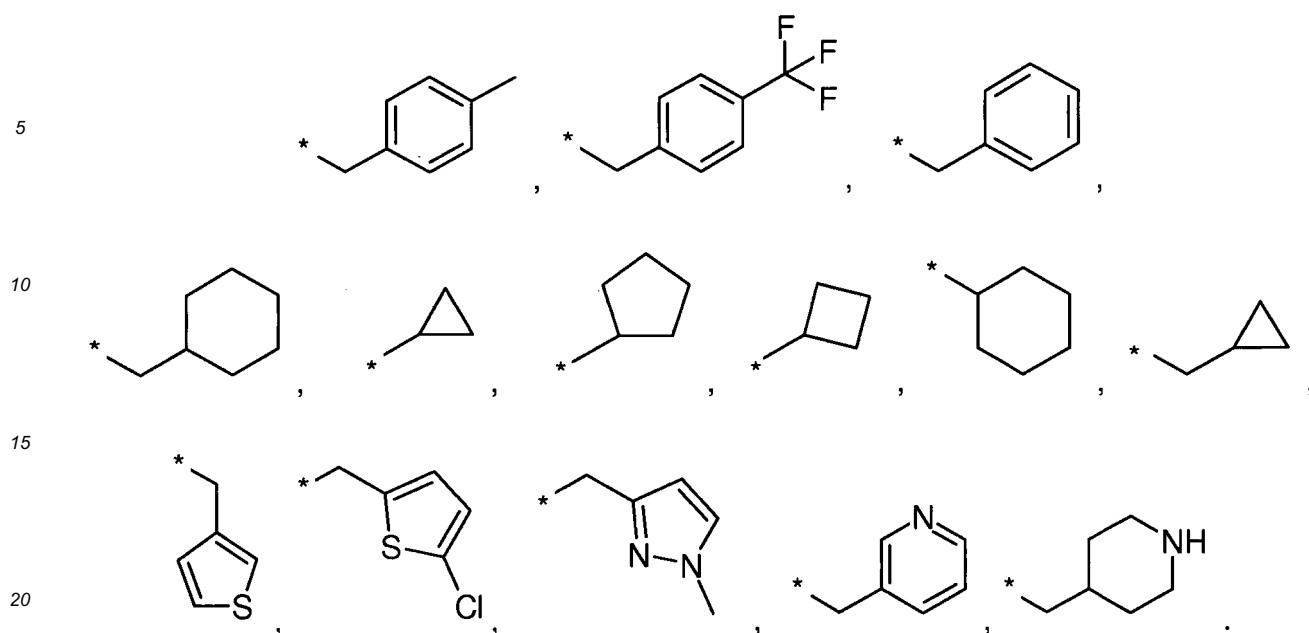
[0081] In a further embodiment R₁₃ is H and

R₁₄ is H, (C₁-C₆)alkyl or (C₃-C₈)cycloalkyl

wherein (C₁-C₆)alkyl or (C₃-C₈)cycloalkyl are unsubstituted.

55 **[0082]** Most preferred R₁₃ and R₁₄ are H.

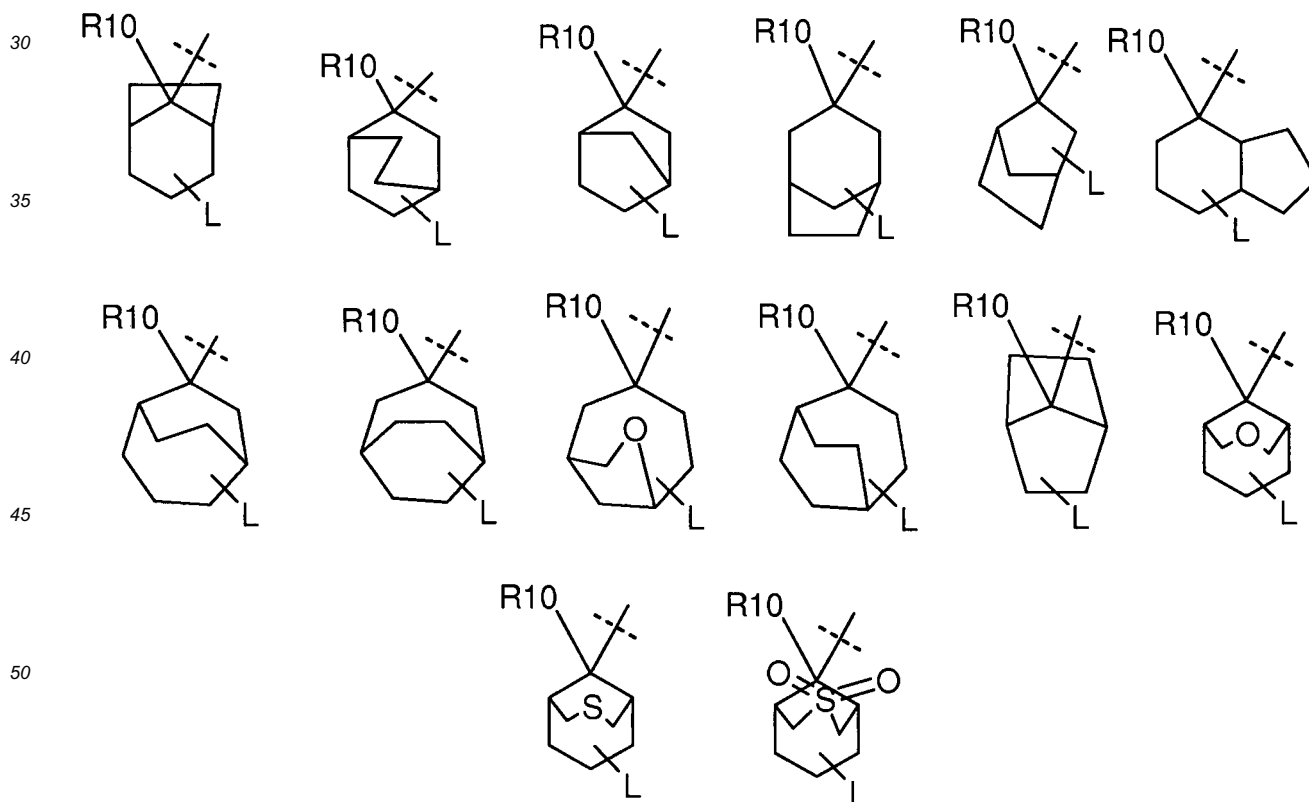
[0083] As examples for the before mentioned embodiments, R₁₃ or R₁₄ are, independently from each other, hydrogen, methyl, ethyl, propyl, isopropyl, 3-methyl-butyl, 2-methylpropyl, butyl, pentyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl or a substituent selected from the group consisting of



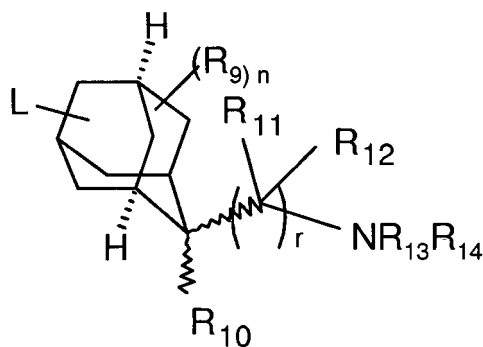
[0084] The asterisk (*) denotes where the bond is connected to the N-atom of the amine.

[0085] A R_{15} residue is described which is H or (C_1-C_6) alkyl, which is unsubstituted or optionally substituted, more preferably R_{15} is H or (C_1-C_4) alkyl, most preferably H. Preferably, the alkyl is unsubstituted.

[0086] In one embodiment of a compound of formula (I) R_6 is absent or the bicyclus or the adamantane formed with R_6 is selected from the group of

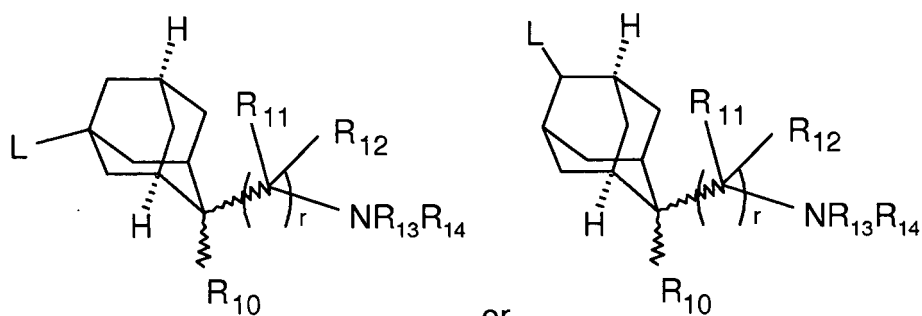


(the bond with the dotted line indicates the position of the $-(CR_{11}R_{12})_rNR_{13}R_{14}$ residue)
or

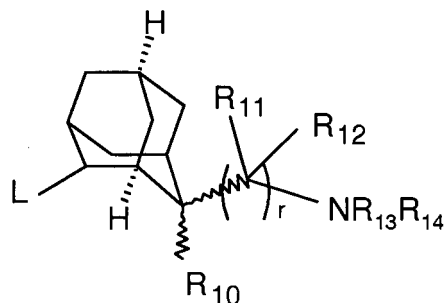


which is unsubstituted or optionally substituted by R_9 . In a preferred embodiment the bicyclus or adamantane is unsubstituted (n is 0) or is substituted once ($n = 1$).

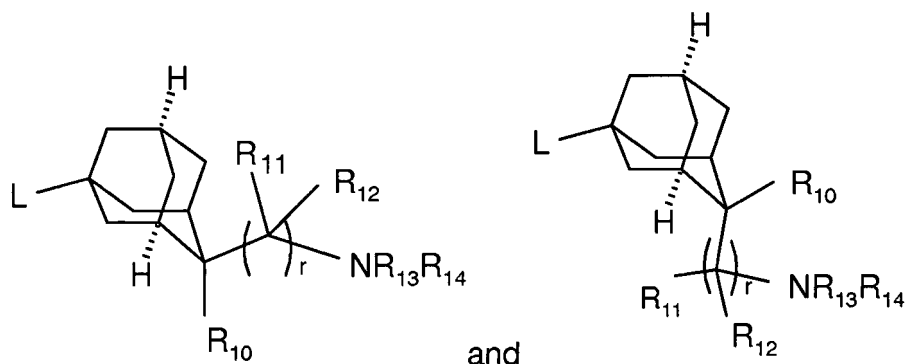
[0087] Preferably the unsubstituted or substituted adamantane has the following structure



or



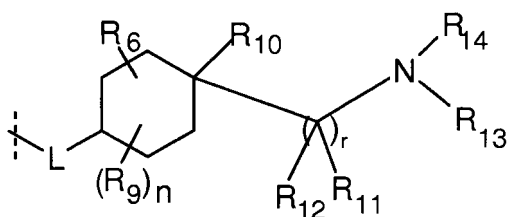
The cis and trans isomers in these adamantane residues such as for example in the structures



are included.

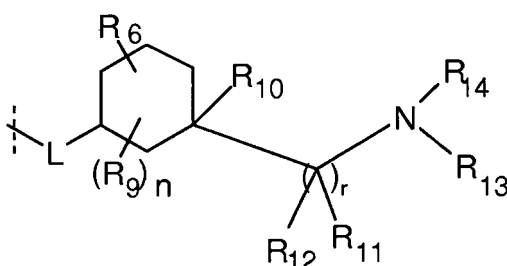
In one embodiment of a compound of formula (I) R_6 is absent, i.e. no bicyclus or adamantane is formed.

[0088] In one embodiment m is 2 and s is 2 resulting in a residue within a compound of formula (I) of the formula



in all their stereochemical forms.

[0089] In another embodiment m is 3 and s is 1 resulting in a residue within a compound of formula (I) of the formula



[0090] In a further embodiment m is 2 and s is 1. In still another embodiment m is 3 and s is 0. In yet another embodiment m is 4 and s is 0.

[0091] In one embodiment of a compound of formula (I) n is 0, 1, or 2. More preferred, n is 0 or 1. Most preferred n is 0.

[0092] In a preferred embodiment r is 1.

[0093] It is described that L is $O(CH_2)_p$. L is $S(CH_2)_p$, $S(O)(CH_2)_p$ or $SO_2(CH_2)_p$ is also described. It is described that L is $NH(CH_2)_p$, $N[(C_1-C_6)alkyl](CH_2)_p$, $N[(C_3-C_6)cycloalkyl](CH_2)_p$, $N[(C_1-C_3)alkylene-aryl](CH_2)_p$ or $N[(C_1-C_3)alkylene-(C_5-C_6)heteroaryl](CH_2)_p$ with $NH(CH_2)_p$, $N(C_1-C_6)alkyl-(CH_2)_p$ being more preferred. A preferred $N(C_1-C_6)alkyl$ is $N(C_1-C_4)alkyl$, more preferably NCH_3 or NCH_2CH_3 with NCH_3 being more preferred is described. L is $S(CH_2)_p$ is described. L is $NH(CH_2)_p$ is also described. Most preferred L is O , S or NH with O being especially preferred.

[0094] p is 0, 1, 2, or 3, more preferred 0 or 1, with 0 being most preferred is described;

[0095] More preferably, m is 2 and s is 2 and L is O , S or NH , preferably O .

[0096] In a further embodiment the present invention relates to a compound of formula (I) selected from the group consisting of

- 6-[4-(1-Amino-propyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
- 6-[4-(1-Amino-cyclopropyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
- 6-[4-(1-Amino-butyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
- 6-[4-(1-Amino-butyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
- 6-[4-(1-Amino-propyl)-4-(4-bromo-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
- 6-[4-(1-Amino-propyl)-4-(2-bromo-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
- 6-[4-(1-Amino-propyl)-4-(4-trifluoromethyl-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
- 6-[4-(1-Amino-propyl)-4-(2-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
- 6-[4-(1-Amino-propyl)-4-(2-chloro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
- 6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-methyl-2H-isoquinolin-1-one,
- 6-[4-(1-Amino-ethyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
- 6-[4-(1-Amino-phenyl-methyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
- 6-[4-(1-Amino-2-methyl-propyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
- 6-[4-(1-Amino-3-methyl-butyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
- 6-[4-(1-Amino-phenyl-methyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
- 6-[4-(1-Amino-1-methyl-ethyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
- 6-[4-(1-Amino-cyclopropyl)-4-(2-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
- 6-[4-(1-Amino-ethyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
- 6-[4-(1-Amino-1-methyl-ethyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
- 6-[4-amino(cyclopropyl)methyl]-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,

6-[4-(1-Amino-propyl)-4-(4-isopropyl-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-propyl)-4-(3-methoxy-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-propyl)-4-(3-bromo-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-2-methyl-propyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, or
 6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-4-bromo-7-chloro-2H-isoquinolin-1-one;

their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts thereof.

[0097] In a further embodiment a compound of formula (I) is selected from the group consisting of

cis-6-[4-(1-Amino-propyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-amino-propyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-on,
 cis-6-[4-(1-Amino-cyclopropyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-aminopropyl)-4-phenylcyclohexyl]oxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-amino-propyl)-4-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-butyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Amino-butyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-butyl)-4-(4-fluoro-phenyl)-cyclo-hexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Amino-butyl)-4-(4'-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amin-propyl)-4-(4-bromo-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(2-bromo-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(4-trifluoromethyl-phenyl)-cyclo-hexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(2-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(2-chloro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-methyl-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-ethyl)-4-(4-fluoro-phenyl)-cyclo-hexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Amino-ethyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3-bromo-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Amino-propyl)-4-(3-bromo-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3-methoxy-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Amino-propyl)-4-(3-methoxy-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(Amino-phenyl-methyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Amino-2-methyl-propyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Amino-3-methyl-butyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(Amino-phenyl-methyl)-4-phenyl-cyclo-hexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Amino-1-methyl-ethyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-cyclopropyl)-4-(2-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-ethyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-1-methyl-ethyl)-4-phenyl-cyclo-hexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-[amino(cyclopropyl)methyl]-4-phenyl-cyclo-hexyl]oxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(4-isopropyl-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-2-methyl-propyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, and
 cis-6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-4-bromo-7-chloro-2H-isoquinolin-1-one,
 and their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts thereof.

[0098] In a further embodiment a compound of formula (I) is selected from the group of

trans-6-[4-((S)-Amino-phenyl-methyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-((R)-Amino-phenyl-methyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,

cis-6-[4-((S)-1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-((R)-1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,

cis-6-[4-((S)-Amino-cyclopropyl-methyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-((R)-Amino-cyclopropyl-methyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,

cis-6-[4-((R)-Amino-cyclopropyl-methyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-((S)-Amino-cyclopropyl-methyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,

cis-6-[4-((S)-1-Amino-ethyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-((R)-1-Amino-ethyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,

6-[4-[(S)-Amino-(4-fluoro-phenyl)-methyl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[(R)-Amino-(4-fluoro-phenyl)-methyl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,

cis-6-[4-((R)-1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, and
 cis-6-[4-((S)-1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, their tautomeric forms and/or

pharmaceutically acceptable salts thereof.

[0099] In a further embodiment a compound of formula (I) is selected from the group consisting of

cis-6-[4-(1-Amino-propyl)-4-pyridin-2-yl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(2,4-difluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(4-fluoro-2-methyl-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3,5-difluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 5 cis-6-[4-(1-Amino-propyl)-4-(3,4-difluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-o-tolyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(2-trifluoromethoxy-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(4-fluoro-3-methoxy-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3-ethoxy-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 10 cis-6-[4-(1-Amino-propyl)-4-(3-methoxy-4-methyl-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3,4-difluoro-phenyl)-cyclohexyloxy]-7-methyl-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3,5-difluoro-phenyl)-cyclohexyloxy]-7-fluoro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3,4-difluoro-phenyl)-cyclohexyloxy]-7-fluoro-5-methyl-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3,5-difluoro-phenyl)-cyclohexyloxy]-7-methoxy-2H-isoquinolin-1-one,
 15 cis-6-[4-(1-Amino-propyl)-4-(2-methoxy-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(4-trifluoro-methoxy-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-1-methyl-ethyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3,5-difluoro-phenyl)-cyclohexyloxy]-4-benzyl-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3,5-difluoro-phenyl)-cyclohexyloxy]-5-chloro-2H-isoquinolin-1-one,
 20 cis-6-[4-(1-Amino-propyl)-4-(3,5-difluoro-phenyl)-cyclohexyloxy]-5,7-dimethyl-2H-isoquinolin-1-one,
 cis-6-[4-(Amino-cyclopropyl-methyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3-trifluoromethyl-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3-trifluoromethoxy-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3-trifluoromethoxy-phenyl)-cyclohexyloxy]-7-methyl-2H-isoquinolin-1-one,
 25 cis-6-[4-(1-Amino-propyl)-4-(3-trifluoromethyl-phenyl)-cyclohexyloxy]-7-methyl-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-fluoro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-fluoro-5-methyl-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-4-benzyl-7-chloro-2H-isoquinolin-1-one,
 cis-4-[1-(1-Amino-propyl)-4-(7-chloro-1-oxo-1,2-dihydro-isoquinolin-6-yloxy)-cyclohexyl]-benzonitrile,
 30 cis-3-[1-(1-Amino-propyl)-4-(7-chloro-1-oxo-1,2-dihydro-isoquinolin-6-yloxy)-cyclohexyl]benzonitrile,
 6-[cis-4-(1-Amino-propyl)-4-(3-methanesulfonyl-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[(1S,4S,5S)-5-(1-Amino-propyl)-5-phenyl-bicyclo[2.2.1]hept-2-yloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[(1R,4R,5R)-5-(1-Amino-propyl)-5-phenyl-bicyclo[2.2.1]hept-2-yloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Benzylamino-propyl)-4-phenyl-cyclohexyloxy]-7-methyl-2H-isoquinolin-1-one,
 35 cis-6-[4-(1-Diethylamino-propyl)-4-phenyl-cyclohexyloxy]-7-methyl-2H-isoquinolin-1-one,
 cis-7-Methyl-6-[4-(1-propylamino-propyl)-4-(3-trifluoromethyl-phenyl)-cyclohexyloxy]-2H-isoquinolin-1-one,
 cis-6-[4-(1-Benzylamino-propyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-7-Chloro-6-[4-(1-isobutylamino-propyl)-4-phenyl-cyclohexyloxy]-2H-isoquinolin-1-one,
 cis-6-[4-(1-Butylamino-propyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 40 cis-7-Chloro-6-[4-[1-(cyclopropylmethyl-amino)-propyl]-4-phenyl-cyclohexyloxy]-2H-isoquinolin-1-one,
 cis-6-[4-(2-Amino-propyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(2-Amino-butyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-2-fluoro-ethyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-3-methoxy-propyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 45 6-[3-(1-Amino-propyl)-3-(4-fluoro-phenyl)-cyclobutyloxy]-7-chloro-2H-isoquinolin-1-one, and
 6-[3-(1-Amino-propyl)-3-(4-fluoro-phenyl)-cyclopentyloxy]-7-chloro-2H-isoquinolin-1-one,
 and their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts thereof.

[0100] In a further embodiment a compound of formula (I) is selected from the group consisting of
 cis-1-[4-(7-Chloro-isoquinolin-6-yloxy)-1-(3,4-difluoro-phenyl)-cyclohexyl]-propylamine,
 50 cis-1-[4-(7-Bromo-isoquinolin-6-yloxy)-1-(3,4-difluoro-phenyl)-cyclohexyl]-propylamine,
 cis-1-[1-(3,5-Difluoro-phenyl)-4-(5,7-dimethyl-isoquinolin-6-yloxy)-cyclohexyl]-propylamine,
 cis-1-[1-(3,5-Difluoro-phenyl)-4-(7-fluoro-5-methyl-isoquinolin-6-yloxy)-cyclohexyl]-propylamine,
 cis-1-[1-(3,4-Difluoro-phenyl)-4-(7-fluoro-isoquinolin-6-yloxy)-cyclohexyl]-propylamine,
 cis-1-[4-(7-Chloro-isoquinolin-6-yloxy)-1-(3,5-difluoro-phenyl)-cyclohexyl]-propylamine,
 55 cis-1-[4-(5-Chloro-isoquinolin-6-yloxy)-1-(3,5-difluoro-phenyl)-cyclohexyl]-propylamine,
 cis-1-[4-(7-Chloro-isoquinolin-6-yloxy)-1-phenyl-cyclohexyl]-propylamine,
 cis-1-[4-(5,7-Dimethyl-isoquinolin-6-yloxy)-1-phenyl-cyclohexyl]-propylamine,
 cis-1-[4-(7-Fluoro-isoquinolin-6-yloxy)-1-phenyl-cyclohexyl]-propylamine,

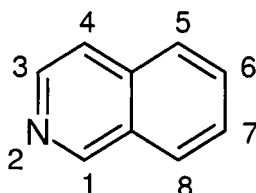
cis-1-[4-(5-Chloro-isoquinolin-6-yloxy)-1-phenyl-cyclohexyl]-propylamine,
 cis-1-[4-(7-Fluoro-5-methyl-isoquinolin-6-yloxy)-1-phenyl-cyclohexyl]-propylamine,
 cis-1-[4-(7-Bromo-isoquinolin-6-yloxy)-1-phenyl-cyclohexyl]-propylamine,
 cis-1-[4-(7-Methyl-isoquinolin-6-yloxy)-1-phenyl-cyclohexyl]-propylamine,
 cis-6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-chloro-isoquinolin-1-ylamine,
 [4-(1-Amino-propyl)-4-(4-methoxy-phenyl)-cyclohexyl]-isoquinolin-6-yl-amine, and
 1-Amino-[4-(1-amino-propyl)-4-(4-methoxy-phenyl)-cyclohexyl]-isoquinolin-6-yl-amine,
 and their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts thereof.

In a further embodiment the present invention relates to a compound of formula (I) selected from the group consisting of
 6-[4-(1-Amino-1-phenyl-ethyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[Amino-(4-methoxy-phenyl)-methyl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[Amino-(4-fluoro-phenyl)-methyl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(Amino-p-tolyl-methyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, or
 6-[4-(Amino-phenyl-methyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts thereof.

[0101] In a further embodiment a compound of formula (I) is selected from the group consisting of
 6-[4-[1-Amino-1-(4-fluoro-phenyl)-ethyl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[1-Amino-1-(4-methoxy-phenyl)-ethyl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[1-Amino-1-cyclopentyl-ethyl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[1-Amino-1-ethyl-propyl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[1-Amino-1-cyclopropyl-ethyl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[1-Amino-1-n-propyl-ethyl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-propyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, and
 6-[4-(Amino-cyclopropyl-methyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts thereof.

[0102] In any embodiments of the present invention one or more or all of the groups contained in the compounds of formula (I) can independently of each other have any of the preferred, more preferred or most preferred definitions of the groups specified above or any one or some of the specific denotations which are comprised by the definitions of the groups and specified above, all combinations of preferred definitions, more preferred or most preferred and/or specific denotations being a subject of the present invention. Also with respect to all preferred embodiments the invention includes the compounds of the formula (I) in all stereoisomeric forms and mixtures of stereoisomeric forms in all ratios, and their pharmaceutically acceptable salts.

[0103] Isoquinoline substitution pattern is numbered according to IUPAC rules:



[0104] The term isoquinolone and isoquinolinone are used synonymously.

All references to "compound(s) of formula (I)" herein refer to compound(s) of the formula (I), (II) (IIIa), (IIIb) and (IV) as described above, and their pharmaceutically acceptable salts, and/or to their stereoisomeric forms, polymorphs and solvates. Physiologically functional derivatives as described herein are also included.

[0105] Pharmaceutically acceptable salts of compounds of the formula (I) mean both their organic and inorganic salts as described in Remington's Pharmaceutical Sciences (17th edition, page 1418 (1985)). Because of the physical and chemical stability and the solubility, preference is given for acidic groups inter alia to sodium, potassium, calcium and ammonium salts; preference is given for basic groups inter alia to salts of maleic acid, fumaric acid, succinic acid, malic acid, tartaric acid, methylsulfonic acid, hydrochloric acid, sulfuric acid, phosphoric acid or of carboxylic acids or sulfonic acids, for example as hydrochlorides, hydrobromides, phosphates, sulfates, methanesulfonates, acetates, lactates, maleates, fumarates, malates, gluconates, and salts of amino acids, of natural bases or carboxylic acids. The preparation of pharmaceutically acceptable salts from compounds of the formula (I) which are capable of salt formation, including their stereoisomeric forms, takes place in a manner known per se. The compounds of the formula (I) form stable alkali metal, alkaline earth metal or optionally substituted ammonium salts with basic reagents such as hydroxides, carbonates, bicarbonates, alcoholates and ammonia or organic bases, for example trimethyl- or triethylamine, ethanolamine, diethanolamine or triethanolamine, trometamol or else basic amino acids, for example lysine, ornithine or arginine. Where

the compounds of the formula (I) have basic groups, stable acid addition salts can also be prepared with strong acids. Suitable pharmaceutically acceptable acid addition salts of the compounds of the invention are salts of inorganic acids such as hydrochloric acid, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acid, and of organic acids such as, for example, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p-toluenesulfonic and tartaric acid. The hydrochloride salt is a preferred salt.

[0106] Salts with a pharmaceutically unacceptable anion such as, for example, trifluoroacetate likewise belong within the framework of the invention as useful intermediates for the preparation or purification of pharmaceutically acceptable salts and/or for use in nontherapeutic, for example in vitro, applications.

[0107] The present invention also includes physiologically functional derivatives of a compound of formula (I). A physiologically functional derivative as used herein refers to any physiologically tolerated derivative of a compound of the formula (I) of the invention, for example an N-oxide, which on administration to a mammal such as, for example, a human is able to form (directly or indirectly) a compound of the formula (I) or an active metabolite thereof.

[0108] Physiologically functional derivatives include prodrugs of the compounds of the invention, as described, for example, in H. Okada et al., Chem. Pharm. Bull. 1994, 42, 57-61. Such prodrugs can be metabolized in vivo to a compound of the invention. These prodrugs may themselves be active or not.

[0109] The invention relates to compounds of the formula (I) in the form of their stereoisomeric forms, which include racemates, enantiomerically enriched mixtures, pure enantiomers and diastereomers and mixtures in any ratio thereof.

[0110] The compounds of the invention may also exist in various polymorphous forms, for example as amorphous and crystalline polymorphous forms. All polymorphous forms of the compounds of the invention belong within the framework of the invention and are a further aspect of the invention.

[0111] If radicals or substituents may occur more than once in the compounds of the formula (I), they may all, independently of one another, have the stated meaning and be identical or different.

[0112] The present invention also relates to the compounds of the formula (I) and/or their pharmaceutically acceptable salts and/or their prodrugs for use as pharmaceuticals (or medicaments), to the use of the compounds of the formula (I) and/or their pharmaceutically acceptable salts and/or their prodrugs for the production of pharmaceuticals for the treatment and/or prevention of diseases associated with Rho-kinase and/or Rho-kinase mediated phosphorylation of myosin light chain phosphatase, i.e. for the treatment and/or prevention of hypertension, pulmonary hypertension, ocular hypertension, retinopathy, and glaucoma, peripheral circulatory disorder, peripheral arterial occlusive disease (PAOD), coronary heart disease, angina pectoris, heart hypertrophy, heart failure, ischemic diseases, ischemic organ failure (end organ damage), fibroid lung, fibroid liver, liver failure, nephropathy, including hypertension-induced, non-hypertension-induced, and diabetic nephropathies, renal failure, fibroid kidney, renal glomerulosclerosis, organ hypertrophy, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome, thrombotic disorders, stroke, cerebral vasospasm, cerebral ischemia, pain, e.g. neuropathic pain, neuronal degeneration, spinal cord injury, Alzheimer's disease, premature birth, erectile dysfunction, endocrine dysfunctions, arteriosclerosis, prostatic hypertrophy, diabetes and complications of diabetes, metabolic syndrome, blood vessel restenosis, atherosclerosis, inflammation, autoimmune diseases, AIDS, osteopathy such as osteoporosis, infection of digestive tracts with bacteria, sepsis, cancer development and progression, e.g. cancers of the breast, colon, prostate, ovaries, brain and lung and their metastases.

[0113] In a further embodiment the invention also relates to the use of a compound of formula (I) and/or a pharmaceutically acceptable salt thereof for the treatment and/or prevention of hypertension, pulmonary hypertension, fibroid liver, liver failure, nephropathy, renal failure, chronic obstructive pulmonary disease (COPD), cerebral vasospasm, pain, spinal cord injury, erectile dysfunction, blood vessel restenosis, or cancer development and progression.

[0114] In a further embodiment the invention also relates to the use of a compound of formula (I) and/or a pharmaceutically acceptable salt thereof for curative approaches associated with stem cell or induced pluripotent stem cell treatment, improvement of recognition or for treatment or prevention of depression, epilepsy, fibroid heart, renal papillary necrosis, tubulo-interstitial dysfunction, multiple sclerosis, vessel stenosis for example carotid stenosis or lipid disorders.

[0115] The present invention furthermore relates to pharmaceutical preparations (or pharmaceutical compositions) which contain an effective amount of at least one compound of the formula (I) and/or its pharmaceutically acceptable salts and a pharmaceutically acceptable carrier, i. e. one or more pharmaceutically acceptable carrier substances (or vehicles) and/or additives (or excipients).

The pharmaceuticals can be administered orally, for example in the form of pills, tablets, lacquered tablets, coated tablets, granules, hard and soft gelatin capsules, solutions, syrups, emulsions, suspensions or aerosol mixtures. Administration, however, can also be carried out rectally, for example in the form of suppositories, or parenterally, for example intravenously, intramuscularly or subcutaneously, in the form of injection solutions or infusion solutions, microcapsules, implants or rods, or percutaneously or topically, for example in the form of ointments, solutions or tinctures, or in other ways, for example in the form of aerosols or nasal sprays.

[0116] The pharmaceutical preparations according to the invention are prepared in a manner known per se and familiar to one skilled in the art, pharmaceutically acceptable inert inorganic and/or organic carrier substances and/or additives

being used in addition to the compound(s) of the formula (I) and/or its (their) pharmaceutically acceptable salts and/or its (their) prodrugs. For the production of pills, tablets, coated tablets and hard gelatin capsules it is possible to use, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts, etc. Carrier substances for soft gelatin capsules and suppositories are, for example, fats, waxes, semisolid and liquid polyols, natural or hardened oils, etc.

Suitable carrier substances for the production of solutions, for example injection solutions, or of emulsions or syrups are, for example, water, saline, alcohols, glycerol, polyols, sucrose, invert sugar, glucose, vegetable oils, etc. Suitable carrier substances for microcapsules, implants or rods are, for example, copolymers of glycolic acid and lactic acid. The pharmaceutical preparations normally contain about 0.5 to about 90 % by weight of the compounds of the formula (I) and/or their pharmaceutically acceptable salts and/or their prodrugs. The amount of the active ingredient of the formula (I) and/or its pharmaceutically acceptable salts and/or its prodrugs in the pharmaceutical preparations normally is from about 0.5 to about 1000 mg, preferably from about 1 to about 500 mg.

[0117] In addition to the active ingredients of the formula (I) and/or their pharmaceutically acceptable salts and to carrier substances, the pharmaceutical preparations can contain one or more additives such as, for example, fillers, disintegrants, binders, lubricants, wetting agents, stabilizers, emulsifiers, preservatives, sweeteners, colorants, flavorings, aromatizers, thickeners, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants. They can also contain two or more compounds of the formula (I) and/or their pharmaceutically acceptable salts. In case a pharmaceutical preparation contains two or more compounds of the formula (I) the selection of the individual compounds can aim at a specific overall pharmacological profile of the pharmaceutical preparation. For example, a highly potent compound with a shorter duration of action may be combined with a long-acting compound of lower potency. The flexibility permitted with respect to the choice of substituents in the compounds of the formula (I) allows a great deal of control over the biological and physico-chemical properties of the compounds and thus allows the selection of such desired compounds. Furthermore, in addition to at least one compound of the formula (I) and/or its pharmaceutically acceptable salts, the pharmaceutical preparations can also contain one or more other therapeutically or prophylactically active ingredients.

[0118] When using the compounds of the formula (I) the dose can vary within wide limits and, as is customary and is known to the physician, is to be suited to the individual conditions in each individual case. It depends, for example, on the specific compound employed, on the nature and severity of the disease to be treated, on the mode and the schedule of administration, or on whether an acute or chronic condition is treated or whether prophylaxis is carried out. An appropriate dosage can be established using clinical approaches well known in the medical art. In general, the daily dose for achieving the desired results in an adult weighing about 75 kg is from about 0.01 to about 100 mg/kg, preferably from about 0.1 to about 50 mg/kg, in particular from about 0.1 to about 10 mg/kg, (in each case in mg per kg of body weight). The daily dose can be divided, in particular in the case of the administration of relatively large amounts, into several, for example 2, 3 or 4, part administrations. As usual, depending on individual behavior it may be necessary to deviate upwards or downwards from the daily dose indicated.

[0119] Furthermore, the compounds of the formula (I) can be used as synthesis intermediates for the preparation of other compounds, in particular of other pharmaceutical active ingredients, which are obtainable from the compounds of the formula I, for example by introduction of substituents or modification of functional groups.

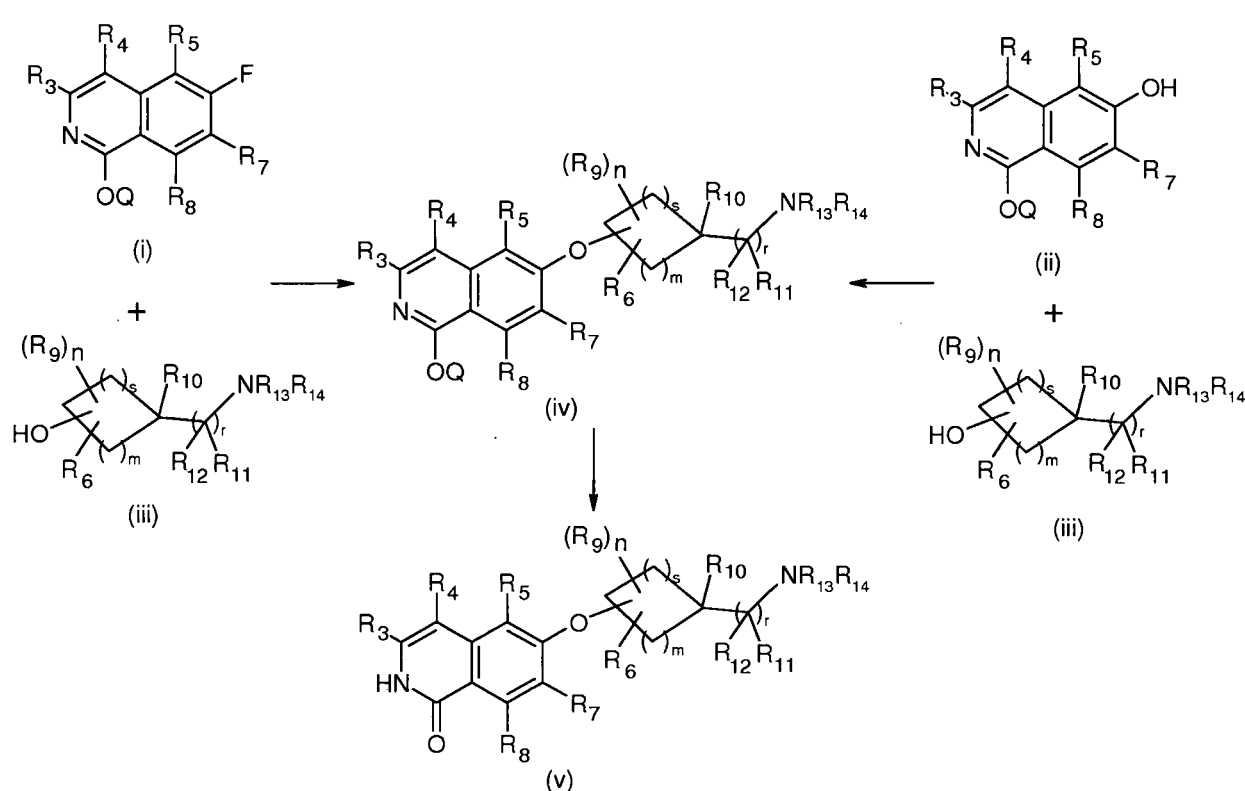
[0120] Compounds of formula (I) may be made in the following manner:

[0121] Compounds of the general formula (I) can be assembled from a suitably substituted isoquinoline moiety and a suitably substituted cycloalkyl amine moiety.

[0122] Isoquinolines and isoquinolones like (i) or (ii), bearing a useful residue for coupling in 6-position, can be obtained by a wide variety of methods, for example reviewed in Alvarez et al. Science of Synthesis 2005, 15, 661-838 and 839-906 and references cited therein. Isoquinolines can also be converted to isoquinolones by methods described in the literature e.g. WO 2007/012421 or WO 2007/012422, like conversion of a suitable isoquinoline into the corresponding N-oxide with an oxidating agent like hydrogen peroxide or metachloro perbenzoic acid and subsequent conversion into the corresponding 1-chloro derivative by a chlorinating agent like phosphorous oxy chloride, followed by displacement of the chlorine by an alcohol under basic condition like sodium methoxide in methanol or conversion into the corresponding 2H-isoquinolone by for example treatment with ammonium acetate in acetic acid at elevated temperature. Also the N-oxide can be directly converted into the corresponding 1-alkoxy derivative by reacting it with a suitable chloroformate in an alcoholic solvent like methanol in presence of a base like triethylamine. It is understood, that the hydroxyl-group in 6-position of (ii) can be liberated at a suitable stage of the synthesis e.g. from treatment of a corresponding 6-methoxy derivative with lewis acids like aluminium chloride or boron tribromide. It is furthermore understood, that 2H-isoquinolones can be converted into suitably protected 1-alkoxy isoquinolones by a variety of methods e.g. treatment of the corresponding 2H-isoquinolones with alkylating agents like benzyl bromide or methyl iodide in the presence of a suitable base like silver carbonate or triethyl amine in a suitable solvent like toluene or THF, or conversion of the said 2H-isoquinolones into their 1-chloro derivatives by treatment with a chlorinating agent like phosphorous oxychloride, followed by displacement of the chlorine by an alcohol e.g. under basic conditions like sodium methoxide in methanol. It is understood, that residues R₃, R₄, R₅, R₇, and/or R₈ can either be incorporated in the starting materials for the synthesis of the respective

isoquinoline or isoquinolone or can be introduced at a suitable later stage e.g. by halogenation like bromination or chlorination and subsequent replacement of said halogen by methods well preceded in the literature like for example Suzuki or Hartwig Buchwald couplings using appropriate catalysts and coupling partners like boronic acids, amines or anilines.

[0123] One possible synthesis for a cycloalkyl amine substituted isoquinolinone (v) with L=O is described below in an exemplary fashion, but does not limit the present invention. The cycloalkyl amine substituted isoquinolinones (for example compound v) can be synthesized via a variety of methods. The following general scheme 1 illustrates some of the possible ways to access the isoquinolinones, but does not limit the present invention.



Scheme 1

[0124] 6-Fluoro-isoquinolones (i), for example substituted by R₃, R₄, R₅, R₇, and/or R₈ being for instance independently from each other substituents like hydrogen, alkyl, alkoxy or halide, can be reacted with suitable R₁₃/ R₁₄ substituted amino alcohols wherein R₁₃ / R₁₄ are independently from each other for example hydrogen, alkyl or a protecting group like for example Boc or Cbz in the presence of base such as DBU, cesium carbonate, or sodium hydride at temperatures ranging from ambient to 100 °C to give the corresponding derivatives (iv). Optionally, this conversion can already be performed at earlier stages of the synthesis (e.g. by reacting a suitable intermediate). It is understood, that this may require in case of unprotected isoquinolones protection on the nitrogen or oxygen of the isoquinolone moiety by suitable methods, like reaction with suitably substituted alkyl or benzyl halides in the presence of base.

[0125] Alternatively, the amino alcohols can be coupled to 6-hydroxy-isoquinolones, such as (ii), under inversion of the hydroxyl bearing carbon center of compounds like (iii), either protected with a suitable protecting group Q or unprotected, via a Mitsunobu reaction using triphenylphosphine and dialkylazodicarboxylates such as diethylazodicarboxylate or diisopropylazodicarboxylate in a suitable solvent like tetrahydrofuran, or toluene. The products like (iv) obtained via these methods can then either be liberated to give compounds of type (v) or, if a suitable amino functionality is present, be reacted with suitable aldehydes or ketones in the presence of a reducing agent like sodium triacetoxy borohydride, sodium borohydride or sodium cyanoborohydride in a suitable solvent and in the presence of a water withdrawing agent like molecular sieves or a suitable ortho ester. This amino group may have to be liberated in an initial step, like for example acidic removal of Boc-groups. Furthermore an amino group can be acylated by reacting it with a suitable acid chloride in the presence of a base like triethyl amine or Hünig's base or by reacting it with a suitable carboxylic acid in the presence of a base like triethylamine or Hünig's base and a coupling reagent like EDC, PyBOP or TOTU.

In case of use of protected isoquinolones, cleavage of the used protection groups is required to liberate the desired isoquinolone (v). This liberation, however, can be performed before or after the reductive amination step, depending on

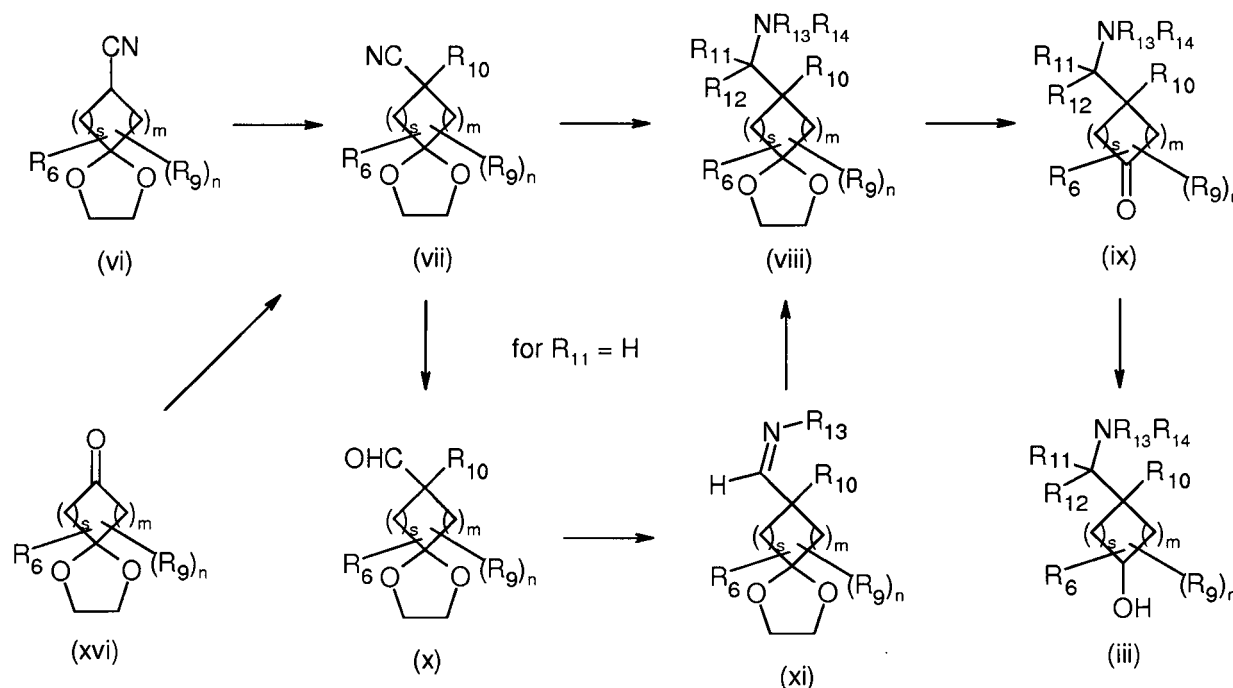
the nature of the used aldehyde / ketone and the protection group used.

Isoquinolone derivatives like (v) can be obtained as free bases or as various salts like for example hydrochlorides, hydrobromides, phosphates, trifluoroacetates, sulfates or fumarates. The salts obtained can be converted into the corresponding free base by either subjecting them to ion exchange chromatography or for example by alkaline aqueous treatment and subsequent extraction with suitable organic solvents like for example methyl tert. butyl ether, chloroform, ethyl acetate or isopropanol/ dichloromethane mixtures and subsequent evaporation to dryness.

[0126] The cycloalkyl amine moieties like for example (iii) can be synthesized via a variety of methods. The following general schemes illustrate some of the possible ways to access the amines, but do not limit the present invention. It is within the abilities of a person skilled in the art to replace the exemplary compounds shown in the schemes and exemplary reagent given in the text by appropriate alternative compounds or reagents or to omit or add synthetic steps when appropriate.

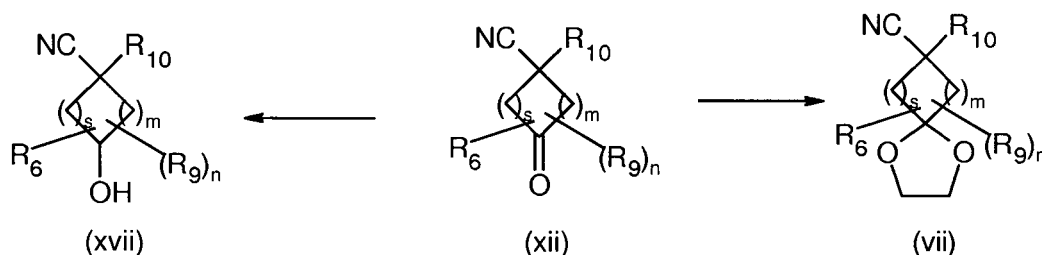
[0127] The synthesis of a cycloalkyl aminoalcohol (iii) is described exemplary in schemes 2 and 3 but does not limit the scope of substituents in the present invention.

A cycloalkyl amine moiety (iii) with a secondary or tertiary amine subunit can for example be accessed starting from a suitably substituted cycloalkylnitrile (vi), which can be substituted with functionalities as alkyl, alkoxy, or acetals. To introduce an residue R_{10} , if wanted, the nitrile can get functionalized in alpha-position by reaction with suitable electrophiles like described in the literature (Organic Process Research & Development, 5(6), 587-592; 2001), using for example a suitable fluorinated aryl compound and a suitable base like KHMDS, LiHMDS or sodium hydride in an inert solvent like toluene. Alternatively, a suitable nucleophile like aryl lithium reagents can be reacted with a suitable ketone (xvi) to give the corresponding alcohol, which can be converted into the corresponding nitrile (vii) by treatment with reagents like TMSCN.



Scheme 2

[0128] Another option is construction of the cycloalkyl moiety for example by Dieckmann condensations like described in the literature (Lednicher et al, J. Med. Chem. 1980, 23(4), 424-30; DeGraffenreid et al., J. Org. Chem. 2007, 72(19), 7455-7458) to give ketones like (xii), that can be converted into their acetals (vii) by treatment with diols like ethylene diol, or can be directly converted into the corresponding alcohols using suitable reductive agents like sodium borohydride in a suitable solvent like methanol, ethanol or THF. The obtained nitrile can then be for example further converted as described in schemes 2 and 4.

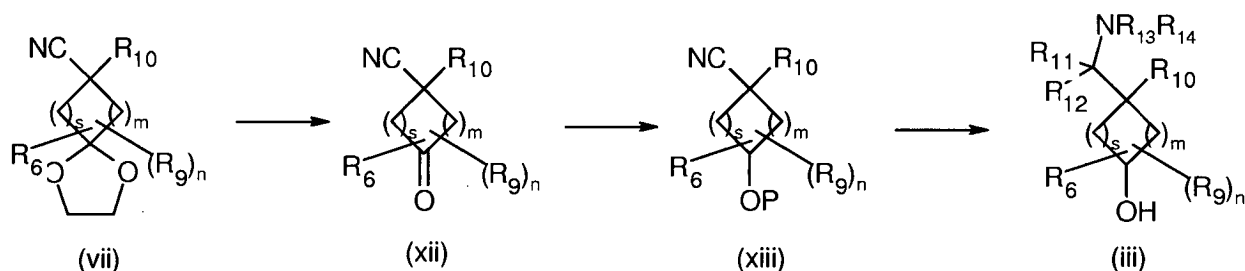


Scheme 3.

[0129] The functionalized nitrile (vii or xvii) can then for example be directly reacted with suitable nucleophiles for the introduction of functional groups R₁₁ and R₁₂, for example lithium organyls or Grignard reagents to give compounds like (viii or iii). A suitable N-protecting group like t-butyloxycarbonyl or benzyloxycarbonyl may or may not be attached after this step depending on the nature of the starting nitrile and the complexity of the reactions to follow. For R₁₁ = R₁₂, lithium organyls can be used as nucleophiles activated by addition of Lewis acids like titanium isopropoxide and cerium chloride.

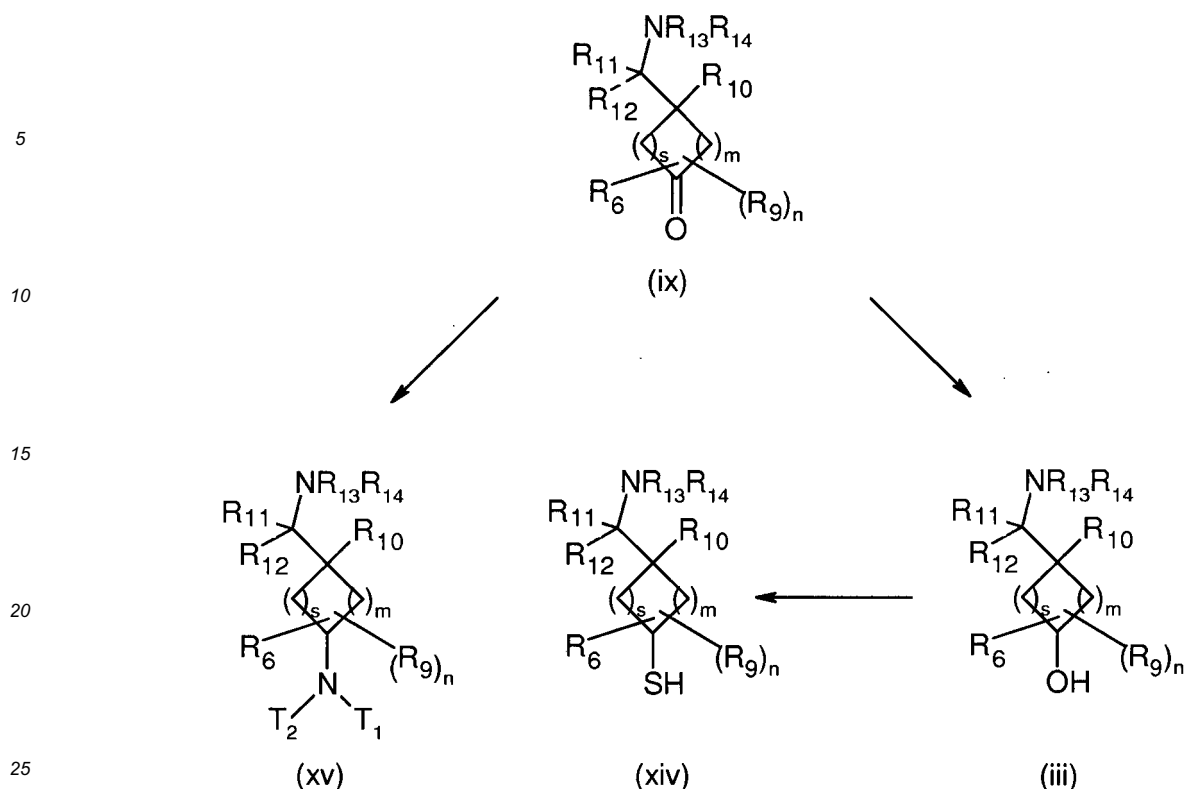
[0130] For R₁₁ is H, the intermediate imine formed on addition of the nucleophiles can be isolated and reduced by suitable reductive agents like cyanoborohydrides or borohydrides in solvents such as tetrahydrofuran or alcohols. Alternatively, the nitrile (vii) can be reduced to the aldehyde (x) by suitable hydride donor reagents like diisobutylaluminumhydride in cold organic solvents such as diethylether or toluene and converted to appropriate imines (xi) like benzylimines or N-tert-butyloxycarbonyl imines via a Lewis acid catalysed reaction with suitably functionalized amines. These imines (xi) can then be reacted with suitable nucleophilic reagents like lithium organyls, Grignard reagents or trimethylsilanes in combination with tetraalkyl fluorides to introduce a variety of substituents like alkyl, cycloalkyl or heterocyclyl groups. The keto functionality can then be liberated by methods known to the person skilled in art, for example by treatment with aqueous acids like acetic acid or hydrochloric acid in acetone mixtures, and subsequently reduced to the corresponding alcohols (iii), generally as cis/trans mixtures, by suitable reducing agents like borohydrides in alcohols, tetrahydrofuran or toluene at deep temperatures.

[0131] This liberation, however, can also be performed after the nitrile functionalization step (Scheme 4), depending on the nature of the used nitrile and the substitution pattern. If the ketone is reduced before the nitrile gets functionalized, generally only one isomer (cis or trans) is obtained in high selectivity. For the conversion of nitriles from type (xiii) to the amines (iii) the use of a suitable protecting group on the alcohol functionality may prove beneficial. Suitable protecting groups are known to the person skilled in art and may be ethers, like tetrahydropyran, methoxymethyl or silyl ethers.



Scheme 4

[0132] To obtain cycloalkyl amino moieties other than cycloalkyl aminoalcohols, various methods can be applied. The following general scheme (scheme 4) illustrates some of the possible ways to access these amines, but does not limit the present invention.



Scheme 5

[0133] For instance, the hydroxy functionality of a compound (iii) can be converted to a thiol via a Mitsunobu reaction using thioacetate and subsequent basic cleavage with a suitable base, leading to amino moieties of type (xiv). These thiols can - after coupling to suitable isoquinolinones under useful reaction conditions like for example in a similar fashion as described above in scheme 1 for the coupling of (iii) - then be used to obtain compounds of formula (I) with the linker unit $L = S$ - or optionally be oxidized via methods known to the person skilled in the art to the corresponding sulfoxides and sulfones (for obtaining compounds of formula (I) with the linker unit $L = SO$ and SO_2). The corresponding amines can be accessed via a reductive amination step starting from ketones such as compound (ix or xii) using suitable amines in the presence of a reducing agent like sodium triacetoxy borohydride, sodium borohydride or sodium cyanoborohydride in the presence of a water withdrawing agent like molecular sieves or a suitable ortho ester.

[0134] In general, protective groups that may still be present in the products obtained in the coupling reaction are then removed by standard procedures. For example, tert-butyl protecting groups, in particular a tert-butoxycarbonyl group which is a protection form of an amino group, can be deprotected, i. e. converted into the amino group, by treatment with trifluoroacetic acid. As already explained, after the coupling reaction also functional groups can be generated from suitable precursor groups. In addition, a conversion into a pharmaceutically acceptable salt or a prodrug of a compound of the formula (I) can then be carried out by known processes.

[0135] In general, a reaction mixture containing a final compound of the formula (I) or an intermediate is worked up and, if desired, the product is then purified by customary processes known to those skilled in the art. For example, a synthesized compound can be purified using well known methods such as crystallization, chromatography or reverse phase-high performance liquid chromatography (RP-HPLC) or other methods of separation based, for example, on the size, charge or hydrophobicity of the compound. Similarly, well known methods such as NMR, IR and mass spectrometry (MS) can be used for characterizing a compound of the invention.

Examples

[0136] The following examples illustrate the various embodiments of the present invention.

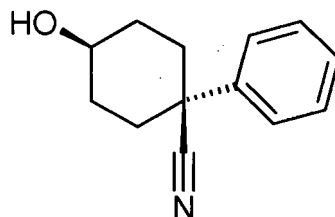
Cis and trans nomenclature in the title of the respective compounds refer to the relative configuration of the - $[CR_{11}R_{12}]NR_{13}R_{14}$ residue and the L-residue at the cycloalkyl ring. This convention is maintained for the respective precursors.

cis-4-Hydroxy-1-phenylcyclohexanecarbonitrile (1)

[0137]

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[0138] To a suspension of 4-cyano-4-phenylcyclohexanone (25 g, 125 mmol) in absolute ethanol (1 L) was added sodium borohydride (9.5 g, 251 mmol) portionwise over 30 minutes. The resulting mixture was stirred at room temperature for 2 hours, ice was then added and the crude mixture stirred for another hour. Ethanol was evaporated under reduced pressure, and the resulting aqueous layer was extracted with dichloromethane. The organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude product cis-4-hydroxy-1-phenylcyclohexanecarbonitrile (25 g, containing approx. 10% of the trans isomer) was used in the next step without any further purification. $R_t = 3.99$ min (Method 8). Detected mass: 202 ($M+H^+$).

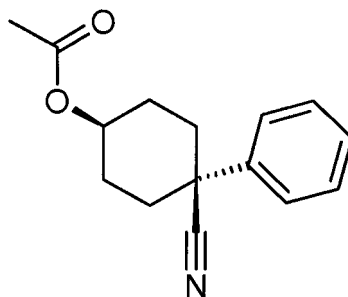
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cis-4-Cyano-4-phenylcyclohexyl acetate (2)

[0139]

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[0140] To a solution of cis-4-hydroxy-1-phenylcyclohexanecarbonitrile (1, 0.2 g, 1 mmol) in anhydrous pyridine (10 mL) were added acetic anhydride (0.1 mL, 1.2 mmol) and 4-dimethylaminopyridine (0.024 g, 0.2 mmol). The reaction mixture was stirred at room temperature for 12 hours, and then evaporated to dryness. A saturated aqueous solution of sodium bicarbonate was added to the crude product and the mixture was extracted with dichloromethane. The organic layer was dried over sodium sulphate, filtered and evaporated to dryness. The crude product was purified by silica gel chromatography (eluting with 0 to 40 % ethyl acetate in cyclohexane) to give 3.39 g of cis-4-cyano-4-phenylcyclohexyl acetate (containing approx. 10% of trans isomer). $R_t = 7.34$ min (Method 9). Detected mass: 266 ($M+Na^+$).

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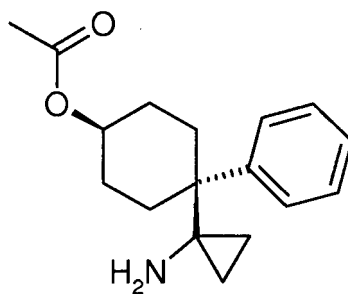
cis-4-(1-Aminocyclopropyl)-4-phenylcyclohexyl acetate (3)

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[0141]

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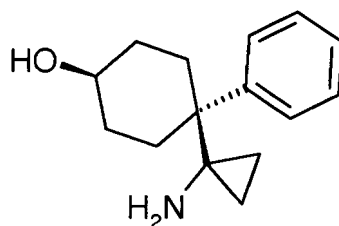
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[0142] A 250-mL three necked round bottom flask equipped with a temperature probe and an argon line was charged with cis-4-cyano-4-phenylcyclohexyl acetate (2, 3.39 g, 13.9 mmol) and anhydrous tetrahydrofuran (140 mL). The resulting solution was cooled to -75°C and titanium (IV) isopropoxide (4.5 mL, 15.3 mmol) was added dropwise while the reaction temperature remained below -70°C. Once the addition was completed, ethylmagnesium bromide (3M in diethyl ether) (10.2 mL, 30.6 mmol) was added dropwise. The mixture was stirred at -70°C for 10 minutes and then allowed to slowly warm to room temperature, while stirring was continued for another 30 minutes. At this stage, boron trifluoride etherate (3.5 mL, 28 mmol) was added, and stirring was continued for 1 hour. Water (14 mL) was added, followed by 10% aqueous HCl (140 mL) and diethyl ether (100 mL). A 10% aq. NaOH solution was added to the resulting clear mixture until the pH became basic. The product was extracted with diethyl ether. The combined organic extracts were dried over anhydrous sodium sulphate. After evaporation of the solvent, the product was purified by flash chromatography on silica gel (eluting with 0 to 100 % ethyl acetate in cyclohexane) to yield 0.65 g of cis-4-(1-aminocyclopropyl)-4-phenylcyclohexyl acetate. R_t = 2.72 min (Method 7). Detected mass: 274 (M+H⁺).

cis-4-(1-Aminocyclopropyl)-4-phenylcyclohexanol (4)

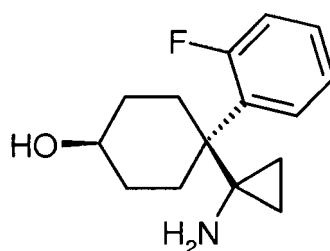
[0143]



[0144] To a solution of cis-4-(1-aminocyclopropyl)-4-phenylcyclohexyl acetate (3, 0.54 g, 2 mmol) in anhydrous methanol (20 mL) was added sodium methoxide (0.5 N in methanol) (8.7 mL, 4.3 mmol). After stirring for 72 hours at room temperature, the reaction mixture was cooled to 0°C, a 1 M solution of hydrochloric acid in diethyl ether (10 mL) was added, and the resulting white precipitate was filtered off. The filtrate was concentrated under reduced pressure, and the resulting crude product was triturated with a methanol/diethyl ether mixture. The beige solid was isolated by filtration to give 400 mg of cis-4-(1-aminocyclopropyl)-4-phenylcyclohexanol as the hydrochloride. R_t = 2.33 min (Method 8). Detected mass: 232 (M+H⁺).

cis-4-(1-Aminocyclopropyl)-4-(2-fluorophenyl)cyclohexanol (5)

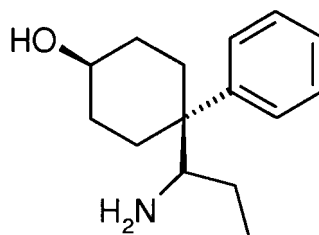
[0145]



[0146] Utilizing the procedures described for the synthesis of 4, 0.219 g of cis-4-(1-aminocyclopropyl)-4-(2-fluorophenyl)cyclohexanol (5) was obtained as the hydrochloride (contaminated with 4% of trans isomer) starting from 4-cyano-4-(2-fluorophenyl)cyclohexanone. R_t = 0.66 min (Method 7). Detected mass: 250 (M+H⁺).

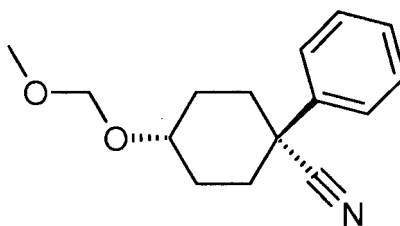
cis-4-(1-Aminopropyl)-4-phenylcyclohexanol (6)

[0147]



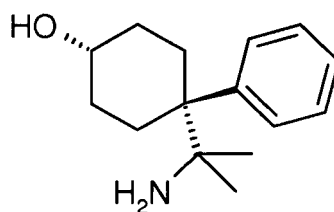
[0148] To a solution of cis-4-hydroxy-1-phenylcyclohexanecarbonitrile (1, 1.0 g, 4.97 mmol) in anhydrous toluene (100 mL) was added dropwise a solution of ethylmagnesium bromide (3M in diethyl ether, 10 mL, 30 mmol). The reaction mixture was refluxed overnight, then poured onto ice. The resulting mixture was extracted with diethyl ether, the organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure. To a solution of this crude product in absolute ethanol (100 mL) was added sodium borohydride (0.257 g, 7.5 mmol). The reaction mixture was stirred at room temperature for 2 hours, aqueous 1 N HCl was then added until pH=1.3. Ethanol was evaporated under reduced pressure, the resulting aqueous phase was washed with diethyl ether, then neutralized with a saturated aqueous sodium bicarbonate solution and eventually extracted with diethyl ether and chloroform, subsequently. The combined organic layers were dried over anhydrous sodium sulphate, filtered and evaporated to dryness. The crude product was dissolved in 15 mL of methanol and HCl (4N in dioxane) (0.9 mL) was added dropwise. The suspension was stirred for 30 min, then evaporated to dryness to yield 0.858 g of cis-4-(1-aminopropyl)-4-phenylcyclohexanol (6) as the hydrochloride (contaminated with 10% of trans isomer). R_t = 2.59 min (Method 8). Detected mass : 234 ($M+H^+$).

cis-4-(Methoxymethoxy)-1-phenylcyclohexanecarbonitrile (7)



[0150] A stirred solution of potassium tert-butoxide (1.6 M in tert-butanol, 37.3 mL, 37.3 mmol) was cooled to 0 °C and anhydrous DMF (6 mL) was added before the mixture began to freeze. A solution of cis-4-hydroxy-1-phenylcyclohexanecarbonitrile (1, 3 g, 14.9 mmol) in anhydrous DMF (30 mL) was added to the reaction mixture. A solution of chloromethyl methyl ether (2.83 mL, 37.3 mmol) was then added dropwise at 2-4°C and the mixture was gradually allowed to warm to room temperature while stirring was continued overnight. The mixture was poured onto cold aqueous sodium bicarbonate solution, then extracted with diethyl ether. The organic layer was dried over sodium sulphate and evaporated. The crude product was purified by chromatography on silica gel to yield 2.2 g of the title compound. R_t = 7.01 min (Method 9). Detected mass: 246 ($M+H^+$)

cis-4-(1-Amino-1-methylethyl)-4-phenylcyclohexanol (8)



[0152] A suspension of commercial anhydrous cerium chloride (Alfa Aesar, 2 g, 8.15 mmol) in anhydrous THF (12 mL) was heated to 45°C for 3 h under vigorous stirring. The slurry was cooled to room temperature and treated with

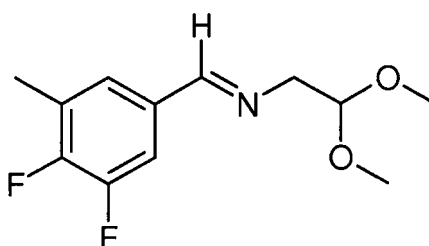
cis-4-(methoxymethoxy)-1-phenylcyclohexanecarbonitrile (7, 1 g, 4.08 mmol). After cooling to -10 °C, a 1.5 M solution of MeLi-LiBr (6.79 mL, 10.2 mmol) in diethyl ether was added dropwise over 20 minutes, then the resulting brown slurry was stirred for an additional 20 min. The reaction was quenched by addition of concentrated NH₄OH (2.6 mL) over 10 min. The yellow suspension obtained was allowed to warm to room temperature, stirred for 30 min, diluted with THF and then filtered. The wet cake was rinsed several times with THF. The combined filtrates were then concentrated to almost dryness, diluted with dichloromethane and washed with 0.1 N NaOH. The organic layer was dried with sodium sulphate and evaporated.

[0153] The crude mixture was suspended in a mixture of methanol (20 mL) and aqueous 2N HCl (20 mL) then stirred overnight at room temperature. After evaporation of methanol and filtration, the filtrate was concentrated to dryness to yield 0.38 g of a crude mixture of the title compound (8). R_t = 2.43 min (Method 9). Detected mass: 234 (M+H⁺).

6,7-difluoro-5-methyl-isoquinoline (43)

a) [1-(3,4-Difluoro-2-methylphenyl)-methylidene]-2,2-dimethoxyamine (40)

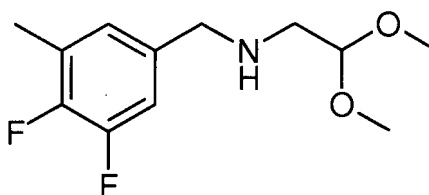
[0154]



[0155] 3,4-difluoro-2-methylbenzaldehyde (26 g, 166 mmol) was dissolved in toluene (182 mL) and reacted with 2-aminoacetaldehyde dimethylacetal (19.3 g, 183 mmol) and toluene sulphonic acid (3.2 g) for 2 hours in a Dean-Stark apparatus. The solution was allowed to cool down, extracted with saturated sodium bicarbonate solution, water and brine, dried over sodium sulphate and evaporated to dryness to give 40.4 g of a dark yellow oil which was used without further purification.

b) 3,4-Difluoro-2-methylbenzyl-2,2-dimethoxyethylamine (41)

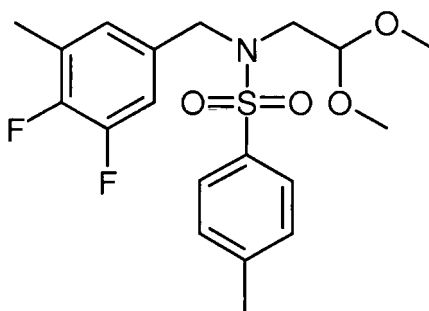
[0156]



[0157] [1-(3,4-Difluoro-2-methylphenyl)-methylidene]-2,2-dimethoxyamine (40, 40.4 g) was dissolved in ethanol (225 mL). Sodium borohydride (4.8 g, 124 mmol) was added portionwise. Stirring was continued overnight. For workup, acetic acid was added until no gas evolution could be observed. Then the solution was evaporated to dryness, taken up in dichloromethane and washed with saturated sodium bicarbonate solution and twice with water. The organic layer was washed with brine, dried over magnesium sulphate and evaporated to dryness. The crude product obtained (37.8 g) was used without purification.

c) N-(3,4-Difluoro-2-methylbenzyl)-N-(2,2-dimethoxyethyl)-4-methylphenylsulphonylamine (42)

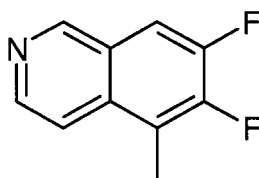
[0158]



[0159] 3,4-Difluoro-2-methylbenzyl-2,2-dimethoxyethylamine (41, 37.8 g) was dissolved in dichloromethane (100 mL). Pyridine (42 mL) was added. At 0 °C a solution of p-toluenesulphonyl chloride (36.8 g, 193 mmol) in dichloromethane was added dropwise. The reaction was allowed to warm to room temperature and stirring continued until conversion was complete. For workup, the reaction mixture was diluted with dichloromethane (100 mL) and extracted twice with 1.5M hydrochloric acid, twice with sodium bicarbonate solution and once with brine. The organic layer was dried over magnesium sulphate, evaporated to dryness to give crude product as an orange oil (68.3 g). This was used without further purification.

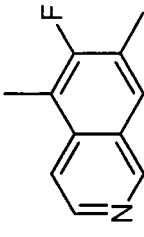
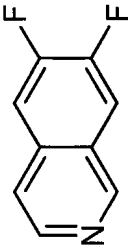
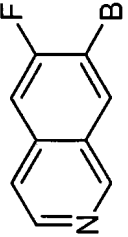
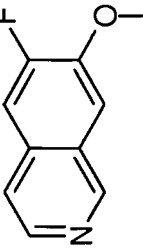
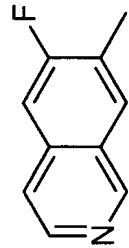
d) 6,7-difluoro-5-methyl-isoquinoline (43)

[0160]



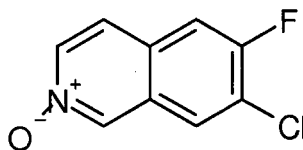
[0161] Aluminium trichloride (112 g, 838 mmol) was suspended in dichloromethane (250 mL) at 0 °C. A solution of N-(3,4-difluoro-2-methylbenzyl)-N-(2,2-dimethoxyethyl)-4-methylphenylsulphonylamine (42, 68.3 g) in dichloromethane (250 mL) was added. The reaction mixture was heated at 50 °C for 2 hours, before being cooled to 0 °C and poured on ice. The organic layer was separated, and the aqueous layer extracted twice more with dichloromethane/isopropanol (3:1). The combined organic phase was extracted twice with saturated sodium bicarbonate solution and dried over magnesium sulphate, before filtration and evaporation gave 63.5 g of crude dark brown semi-solid product. This was purified by chromatography on silica gel. Elution with ethyl acetate/heptane (5%:95% to 35%:65%) gave 11.3 g of the title compound 43 as a tan-coloured solid. R_t = 0.86 min (Method 10). Detected mass: 180.1 ($M+H^+$).

[0162] The Isoquinolines in the following table were obtained by following a similar reaction sequence as used for synthesis of 43.

Comp. No.	Starting compound	Product	Chemical Name	[M+H ⁺]	R _f /[min]	Method
44	3,5-dimethyl-4-fluoro-benzaldehyde		5,7-dimethyl-6-fluoro-isoquinoline	176.1	1.06	10
45	3,4-difluorobenzaldehyde		6,7-difluoro-isoquinoline	166.1	1.07	2
46	3-bromo-4-fluoro-benzaldehyde		7-bromo-6-fluoro-isoquinoline	226.0 228.3	0.91	4
47	4-fluoro-3-methoxybenzaldehyde		6-fluoro-7-methoxy-isoquinoline	178.1	0.90	10
48	4-fluoro-3-methylbenzaldehyde		6-fluoro-7-methylisoquinoline	161.9	0.90	10

7-Chloro-6-fluoro-isoquinoline 2-oxide (9)

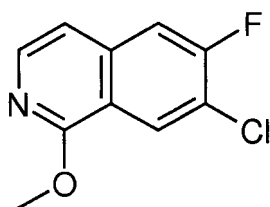
[0163]



[0164] 50 g of 7-chloro-6-fluoro-isoquinoline (prepared according to WO 2007/012422) were dissolved in dichloromethane and cooled to 5 °C. 69.6 g of m-chloro-perbenzoic acid (70%) were added portionwise. The mixture was stirred at room temperature. When conversion was complete, the mixture was diluted with 1.5 L of dichloromethane and washed three times with saturated sodium bicarbonate solution. The organic layer was dried over sodium sulphate and evaporated to dryness to give 47.6 g of the desired product 9. $R_t = 0.98$ min (Method 5). Detected mass: 198.1 ($M+H^+$).

7-Chloro-6-fluoro-1-methoxy-isoquinoline (10)

[0165]



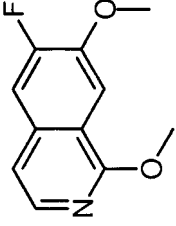
[0166] 10 g of 7-Chloro-6-fluoro-isoquinoline 2-oxide (9) were dissolved in 100 mL of dry methanol. 12 mL of ethyl chloroformate were added dropwise at -10°C. The mixture was allowed to stir for 15 minutes and then 28 mL of triethylamine, dissolved in 55 mL of methanol, were added dropwise at -20 °C over 1 h.

100 mL of 2N aqueous sodium hydroxide solution were added and the formed precipitate was filtered. Additional product was precipitated by addition of 2N sodium hydroxide solution and water to the mother liquor. The combined solids were dried to give 7.8 g of the desired product (10). $R_t = 3.75$ min (Method 1). Detected mass: 212.0 ($M+H^+$).

[0167] The following compounds were obtained in a similar fashion as described for the synthesis of 10, starting from the respective isoquinolines.

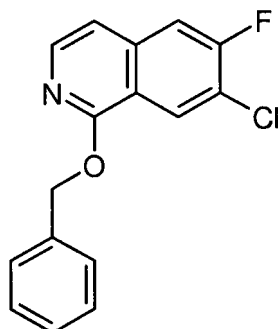
Comp. No.	Starting compound	Product	Chemical Name	[M+H ⁺]	R _f [min]	Method
49	5-Chloro-6-fluoro-isoquinoline		5-Chloro-6-fluoro-1-methoxy-iso-quinoline	212.0	1.78	10
50	45		6,7-difluoro-1-methoxy-isoquinoline	196.1	3.53	1
51	43		6,7-Difluoro-1-methoxy-5-methyl-isoquinoline	210.1	3.85	2
52	48		6-fluoro-1-methoxy-7-methyl-isoquinoline	192.1	3.44	2
53	44		6-Fluoro-1-methoxy-5,7-dimethyl-iso quinoline	206.1	3.74	2

(continued)

Comp. No.	Starting compound	Product	Chemical Name	[M+H ⁺]	R _V [min]	Method
54	47		6-Fluoro-1,7-dimethoxy-isoquinoline	208.1	3.1	2

1-Benzyloxy-7-chloro-6-fluoro-isoquinoline (38)

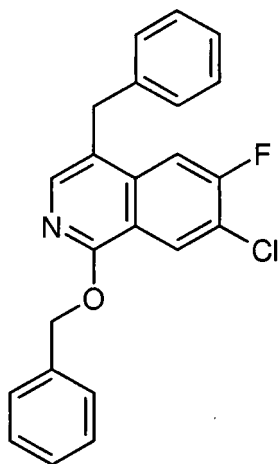
[0168]



[0169] 7-Chloro-6-fluoro-2H-isoquinolin-1-one (prepared according to WO 2007/012422; 52.2 g) was dissolved in THF (1 L). After addition of silver carbonate (145.5 g) and benzyl bromide (40.6 mL), the mixture was stirred at room temperature overnight. Another 6.2 mL of benzyl bromide were added and the mixture was stirred at 70 °C for 2 h. After cooling down to room temperature, the reaction mixture was diluted by addition of 1 L of ethyl acetate and filtered over celite. The filter cake was washed thoroughly, the organic layer was evaporated and subjected to silica gel chromatography (n-heptanes: methyl tert. butyl ether) to give 27.8 g of the title compound (38). $R_t = 3.73$ min (Method 1). Detected mass: 288.1 ($M+H^+$).

1-Benzyloxy-4-benzyl-7-chloro-6-fluoro-isoquinoline (55)

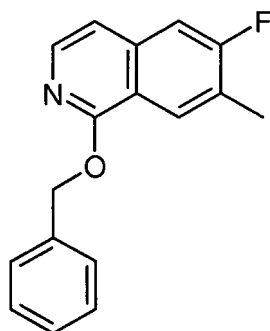
[0170]



[0171] As a side product of the preparation of 1-benzyloxy-7-chloro-6-fluoro-isoquinoline (38), 8.45 g of 1-benzyloxy-4-benzyl-7-chloro-6-fluoro-isoquinoline (55) could be isolated by silica gel chromatography. $R_t = 4.04$ min (Method 1). Detected mass: 378.1 ($M+H^+$).

1-Benzyloxy-7-methyl-6-fluoro-isoquinoline (39)

[0172]

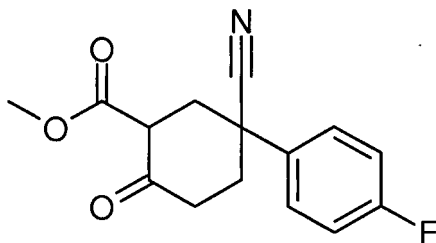


[0173] 1-Benzyloxy-7-methyl-6-fluoro-isoquinoline (39) has been prepared according to the procedure described for the synthesis of (38) starting from 7-methyl-6-fluoro-2H-isoquinolin-1-one (prepared according to the protocol described in WO 2007/012421 or WO 2007/012422). $R_t = 4.00$ min (Method 1). Detected mass: 268.1 ($M+H^+$).

1-(4-Fluoro-phenyl)-4-oxo-cyclohexanecarbonitrile (12)

a) 5-Cyano-5-(4-fluoro-phenyl)-2-oxo-cyclohexanecarboxylic acid methyl ester (11)

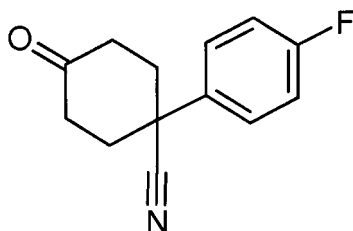
[0174]



[0175] 70 mL of methylacrylate and 50 g of 4-fluorophenylacetonitrile were dissolved in a mixture of 200 mL of THF and 50 mL of dry methanol. 150 mL of sodium methylate (30% in methanol) were added dropwise, while temperature was maintained below 40 °C. The mixture was stirred at room temperature for 15h and heated for another 4h at 50 °C. When the reaction was complete, the mixture was allowed to cool to room temperature and poured onto a cold 2N aqueous hydrochloric acid solution. The aqueous layer was extracted three times with ethyl acetate and the combined organic layer was washed with water and brine, dried over magnesium sulphate and evaporated to give 101.5 g of the desired product. $R_t = 1.59$ min (Method 5). Detected mass: 276.2 ($M+H^+$).

b) 1-(4-Fluoro-phenyl)-4-oxo-cyclohexanecarbonitrile (12)

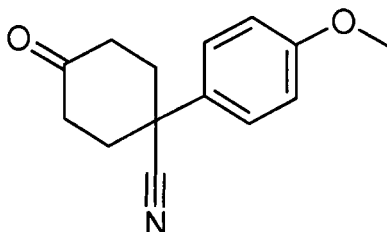
[0176]



[0177] 101.5 g of 5-Cyano-5-(4-fluoro-phenyl)-2-oxo-cyclohexanecarboxylic acid methyl ester (11) were dissolved in 680 mL of ethanol and 171 mL of concentrated aqueous hydrochloric acid were added. The mixture was heated to reflux for 40h, then evaporated. The residue was taken up in water and extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulphate and evaporated to give 95.2 g of crude product, that was purified by silica gel filtration (heptanes:ethyl acetate) to yield 50.4 g of the desired product 12. $R_t = 1.26$ min (Method 1). Detected mass: 218.2 ($M+H^+$).

1-(4-Methoxy-phenyl)-4-oxo-cyclohexanecarbonitrile (56)

[0178]

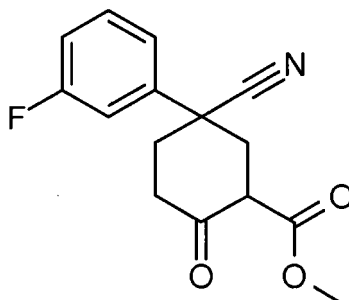


[0179] 56 was obtained from methylacrylate and 4-methoxyphenylacetonitrile in a similar fashion as described for synthesis of (12). $R_t = 4.24$ min (Method 3). Detected mass: 230.1 ($M+H^+$).

1-Cyano-1-(3-fluorophenyl)cyclohexan-4-one (58)

a) 1-Cyano-1-(3-fluorophenyl)-3-methoxycarbonylcyclohexan-4-one (57)

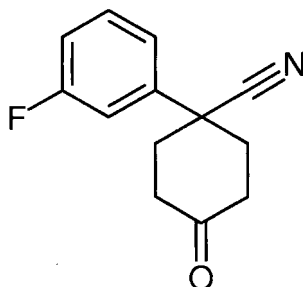
[0180]



[0181] Potassium t-butoxide (62.3 g, 555 mmol) was added dropwise to a solution of 3-fluorophenylacetonitrile (56, 25 g, 185 mmol) in THF (500 mL). The reaction mixture was stirred overnight. The reaction mixture was acidified with hydrochloric acid (3M) and extracted with dichloromethane. The organic extracts were evaporated to yield 57.2 g of an orange oil. $R_t = 3.39$ min (Method 3). Detected mass: 275.1 ($M+H^+$).

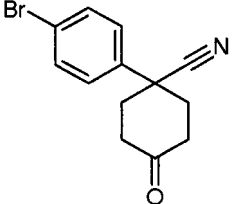
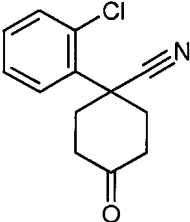
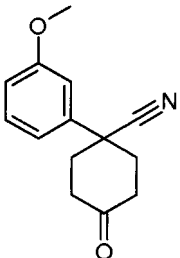
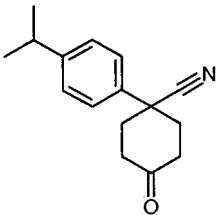
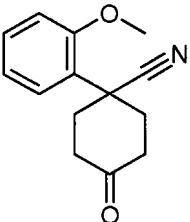
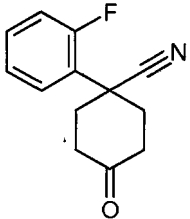
b) 1-Cyano-1-(3-fluorophenyl)cyclohexan-4-one (58)

[0182]



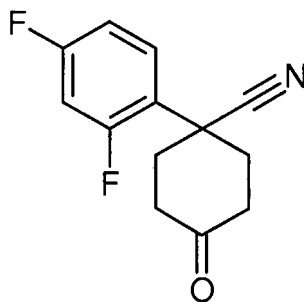
[0183] A mixture of 1-cyano-1-(3-fluorophenyl)-3-methoxycarbonylcyclohexan-4-one (57, 51 g, 185 mmol), water (54.8 mL) and DMSO (840 mL) was heated and stirred at 150 °C for 3 hours, followed by stirring at room temperature overnight. The reaction mixture was evaporated and purified by chromatography on silica gel. Elution with ethyl acetate/heptane (5%:95% to 30%:70%) gave 28 g of desired material as a solid product. $R_t = 3.89$ min (Method 3). Detected mass: 218.2 ($M+H^+$).

[0184] The following cyclohexanones were prepared using the same procedure as described for 58, starting from the respective phenylacetonitrils.

Comp. No.	Starting compound	Product	Chemical Name	[M+H ⁺]	R _f / [min]	Method
59	4-bromo-phenyl acetonitrile		1-cyano-1-(4-bromophenyl) cyclohexan-4-one	277.9	4.79	3
60	2-chloro-phenyl acetonitrile		1-cyano-1-(2-chlorophenyl) cyclohexan-4-one	275.2 (M+ CH ₃ CN +H ⁺)	1.87	4
61	3-methoxyphenyl acetonitrile		1-cyano-1-(3-methoxyphenyl)cyclohexan-4-one	229.1	4.31	6
62	4-isopropylphenyl acetonitrile		1-cyano-1-(4-isopropylphenyl)cyclohexan-4-one	285.3 (M+ CH ₃ CN +H ⁺)	2.23	4
63	2-methoxyphenyl acetonitrile		1-cyano-1-(2-methoxyphenyl)cyclohexan-4-one	230.2	3.81	6
64	2-fluoro-phenyl acetonitrile		1-cyano-1-(2-fluorophenyl) cyclohexan-4-one	259.3 (M+ CH ₃ CN +H ⁺)	1.79	4

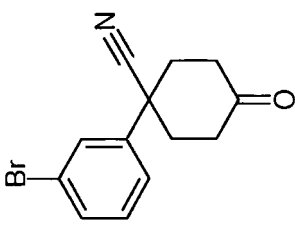
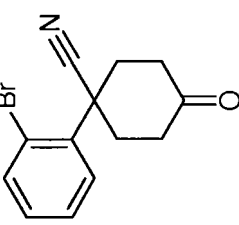
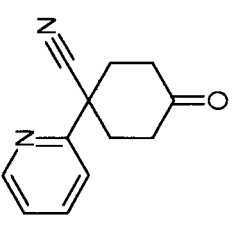
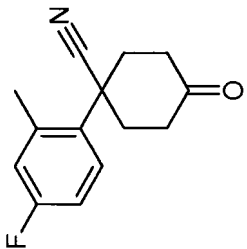
1-Cyano-1-(2,4-difluorophenyl)cyclohexanone (65)

[0185]

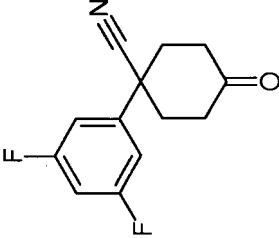
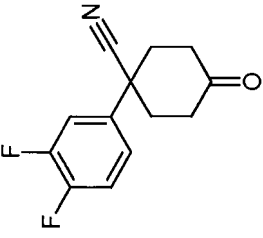
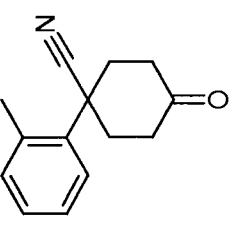


[0186] Potassium t-butoxide (55 g, 489 mmol) was added to a stirred solution of 2,4-difluorophenylacetonitrile (25 g, 163 mmol) and methyl acrylate (28.1 g, 29.4 mL, 326 mmol) in THF (475 mL) at room temperature. After one hour stirring, water (2.4 L) was added and the mixture stirred for 2 hours at 68 °C. After cooling the mixture was extracted with methyl tert butyl ether. After drying over sodium sulphate the organic phase was evaporated to give 34.7 g of an orange oil which was purified by chromatography on silica gel. Elution with ethyl acetate/heptane (5%:95% to 35%:65%) gave the desired product after evaporation as 19 g of a colourless crystalline solid. $R_t = 3.84$ min (Method 3). Detected mass: 236.3 ($M+H^+$).

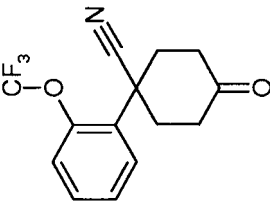
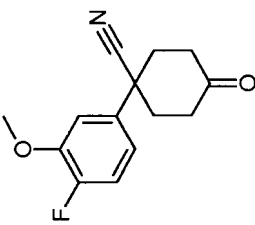
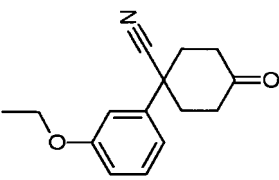
[0187] The following cyclohexanones were prepared using the same procedure as described for 65, starting from the respective phenylacetonitrils:

Comp. No.	Starting compound	Product	Chemical Name	[M+H ⁺]	R _t [min]	Method
66	3-bromophenyl acetonitrile		1-cyano-1-(3-bromophenyl)cyclohexan-4-one	278.1	4.26	18
67	2-bromophenyl acetonitrile		1-cyano-1-(2-bromophenyl)cyclohexan-4-one	302.2 (M+ Na ⁺)	4.45	6
68	Pyrid-2-yl acetonitrile		1-cyano-1-(pyrid-2-yl)cyclohexan-4-one	201.1	1.75	1
69	4-fluor-2-methylphenyl acetonitrile		1-cyano-1-(4-fluoro-2-methylphenyl)cyclohexan-4-one	232.3	4.02	6

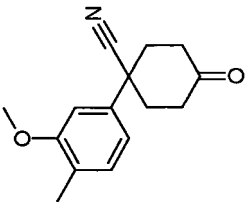
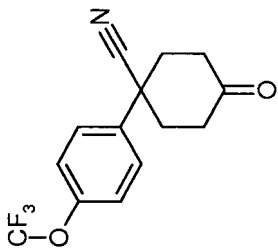
(continued)

Comp. No.	Starting compound	Product	Chemical Name	[M+H ⁺]	R _f /[min]	Method
70	3,5-difluorophenyl acetonitrile		1-cyano-1-(3,5-difluorophenyl) cyclohexan-4-one	236.1	4.02	6
71	3,4-difluorophenyl acetonitrile		1-cyan-1-(3,4-difluorophenyl) cyclohexan-4-one	236.2	3.98	6
72	2-methyl phenyl acetonitrile		1-cyano-1-(2-methylphenyl) cyclohexan-4-one	214.3	3.92	6

(continued)

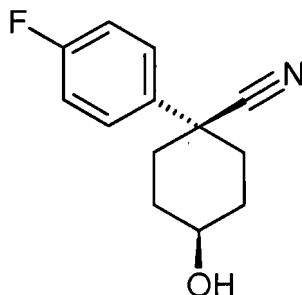
Comp. No.	Starting compound	Product	Chemical Name	[M+H ⁺]	R _f / [min]	Method
73	2-trifluoro methoxy phenyl acetonitrile		1-cyano-1-(2-trifluoromethoxy-phenyl)cyclohexan-4-one	284.1	2.26	20
74	4-fluoro-3-methoxy phenyl acetonitrile		1-cyano-1-(4-fluoro-3-methoxyphenyl)cyclohexan-4-one	248.2	3.89	6
75	3-ethoxy phenyl acetonitrile		1-cyano-1-(3-ethoxyphenyl)cyclohexan-4-one	244.3	4.19	6

(continued)

Comp. No.	Starting compound	Product	Chemical Name	[M+H ⁺]	R _f / [min]	Method
76	3-methoxy-4-methylphenyl acetonitrile		1-cyano-1-(3-methoxy-4-methylphenyl)cyclohexan-4-one	244.0	4.53	6
77	4-trifluoro methoxy phenyl acetonitrile		1-cyano-1-(4-(trifluoromethoxy-phenyl) cyclohexan-4-one	284.2	4.36	6

cis-4-Hydroxy-1-(4-fluoro-phenyl)-cyclohexanecarbonitrile (13)

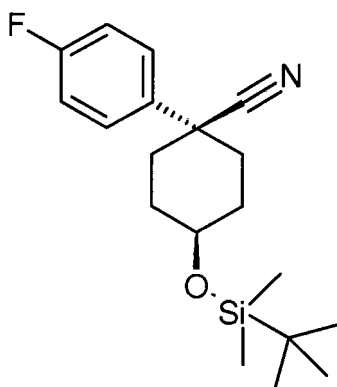
[0188]



[0189] 20 g of 1-(4-Fluoro-phenyl)-4-oxo-cyclohexanecarbonitrile (12) were dissolved in 300 mL of dry ethanol and cooled to -20°C. 3.83 g of sodium borohydride were added and the mixture was allowed to slowly warm to room temperature. When conversion was complete, 150 mL of water were added and the pH was adjusted to 2 by addition of 2N hydrochloric acid. The mixture was extracted with ethyl acetate three times and the combined organic layer was extracted with brine, dried over magnesium sulphate and evaporated to dryness. The resulting residue was crystallized from n-heptanes:ethyl acetate to give 11.9 g of the desired product. $R_t = 2.78$ min (Method 1). Detected mass: 220.1 ($M+H^+$).

cis-4-(tert-Butyl-dimethyl-silanyloxy)-1-(4-fluoro-phenyl)-cyclohexane-carbonitrile (78)

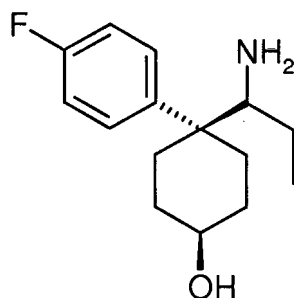
[0190]



[0191] 30 g of cis-4-Hydroxy-1-(4-fluoro-phenyl)-cyclohexanecarbonitrile (13) were dissolved in 350 mL of dry dichloromethane. 39.8 mL of 2,6-lutidine were added and the mixture was cooled to 0°C. 37.7 mL of tert.-butyldimethylsilyl trifluoromethanesulfonate were added and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane, extracted twice with water, 0.1 N hydrochloric acid and once with saturated sodium bicarbonate and brine, dried over magnesium sulphate, evaporated to dryness and purified by silica gel chromatography to give 43.8 g of the desired product. $R_t = 3.21$ min (Method 12). Detected mass: 334.2 ($M+H^+$).

cis-4-(1-amino-propyl)-4-(4-fluoro-phenyl)-cyclohexanol (14)

[0192]



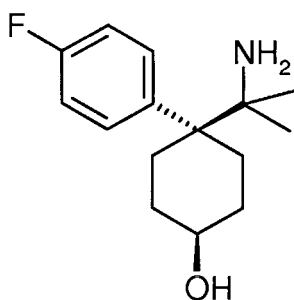
[0193] Under argon, 2 g of cis-4-hydroxy-1-(4-fluoro-phenyl)-cyclohexanecarbonitrile (13) were dissolved with cooling in a 1 M solution of ethyl magnesium bromide in THF (or diethyl ether, alternatively). The reaction mixture was refluxed for 14h, cooled to room temperature and diluted with 600 mL of THF. The mixture was quenched by addition of a minimal amount of methanol, filtered over celite and evaporated to dryness. The resulting foam was dissolved in 300 mL of ethanol and 690 mg of sodium borohydride were added portionwise under cooling. The mixture was allowed to stir until the reaction was complete, evaporated to dryness and the resulting residue was partitioned between 1 N aqueous HCl and ethyl acetate. The organic layer was extracted once with 1 N HCl and the combined aqueous layers were washed with ethyl acetate and subsequently adjusted to pH 12 by addition of 5N sodium hydroxide solution. The aqueous layer was extracted twice with dichloromethane, the combined dichloromethane layers were washed with brine, dried over sodium sulphate and evaporated to give 1.72 g of the desired product. $R_t = 2.25$ min (Method 1). Detected mass: 252.2 ($M+H^+$).

[0194] Alternatively, 14 can be obtained employing 78 in a similar reaction:

18.3 g of 78 were dissolved in 183 mL of dry toluene and 36.6 mL of a solution of ethyl magnesium bromide (3M in diethylether) were added. The mixture was stirred at 80°C for 16h, diluted with THF, cooled to 5°C and quenched by addition of a few mL of ethanol. The mixture was filtered over celite, the solution evaporated to dryness and the residue was taken up in 100 mL of ethanol. 4.15 g of sodium borohydride was added portionwise and stirring was continued overnight. The mixture was evaporated to dryness, the mixture was taken up in dichloromethane and extracted with 2N HCl and brine. The organic layer was evaporated, the residue was taken up in methyl tert.butyl ether and extracted several times with 2N HCl. The combined HCl layers were adjusted to pH 12 by addition of 5N sodium hydroxide and extracted with dichloromethane. The dichloromethane layer was dried over $MgSO_4$ and evaporated to give 13.0 g of the desired product.

cis-4-(1-Amino-1-methyl-ethyl)-4-(4-fluoro-phenyl)-cyclohexanol (79)

[0195]

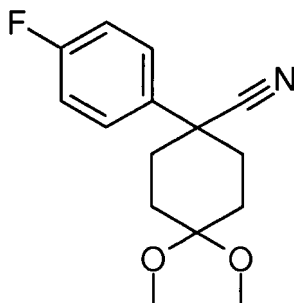


[0196] 300 mg of 78 were dissolved in 10 mL of dry diethyl ether. Then, 0.3 mL of methyl magnesium bromide (3M in diethyl ether) were added. The mixture was cooled to 0°C and 0.85 mL of a solution of methyl lithium (1.6 M) were added. After 1 h, 255 mg of titanium(IV) isopropoxide were added. 10 minutes later 1.4 mL of a solution of methyl lithium (1.6 M) in diethylether were added. The mixture was stirred overnight. Then 5mL of 2N sodium hydroxide were added slowly at 0 °C, 30 mL of methyl tert.butyl ether were added and the NaOH layer was extracted several times with methyl tert.butyl ether. The combined organic layer was dried and evaporated. The resulting residue was dissolved in 5 mL of methyl tert.butyl ether, cooled to 0 °C and 5 mL of 2N hydrochloric acid were added. Stirring was continued overnight, the ether layer was extracted again with 2N hydrochloric acid and the combined aqueous layer was cooled to 0°C and 4 mL of 5N sodium hydroxide solution were added. The aqueous layer was extracted several times with dichloromethane, the

combined dichloromethane layers were dried and evaporated to give 80 mg of the desired product. $R_t = 2.33$ min (Method 3). Detected mass: 217.2 ($M+H^+$)

8-(4-Fluoro-phenyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (15)

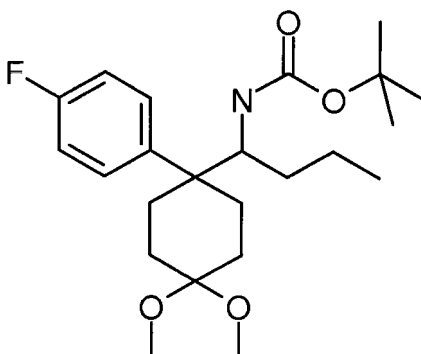
[0197]



[0198] 15 g of 1-(4-Fluoro-phenyl)-4-oxo-cyclohexanecarbonitrile (12) were dissolved in 500 mL of toluene, then 900 mg of p-toluene sulfonic acid were added and the reaction mixture was heated in a Dean-Stark apparatus for 6h. The mixture was allowed to cool to room temperature and washed twice with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated to dryness to yield 17.9 g of the desired product. $R_t = 1.47$ min (Method 5). Detected mass: 262.2 ($M+H^+$).

{1-[8-(4-Fluoro-phenyl)-1,4-dioxaspiro[4.5]dec-8-yl]-butyl}-carbamic acid tert-butyl ester (16)

[0199]

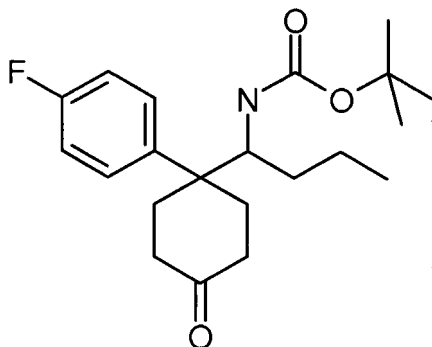


[0200] 1.5 g of 8-(4-Fluoro-phenyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (15) were dissolved in 2.9 mL of a 2M solution of propylmagnesium chloride in diethylether. The mixture was heated under reflux overnight. Another equivalent of propylmagnesium chloride solution was added and heating was continued for another day. The mixture was diluted by diethyl ether (THF could be used alternatively) and a minimal amount of saturated sodium sulphate solution was added. The mixture was filtered over celite and the precipitate was washed with diethyl ether. 490 mg of sodium borohydride was added to the combined organic layer and the mixture was allowed to stir until conversion was complete. A mixture of 2N HCl, brine and water (1:3:6) was added. The phases were separated, the organic layer was extracted twice with the mixture of 2N HCl, brine and water (1:3:6). The combined aqueous layer was adjusted to alkaline pH by addition of 2M sodium hydroxide solution and extracted twice with dichloromethane. The combined dichloromethane layer was washed with brine, and dried over sodium sulphate.

5 mL of triethylamine and 5.86 g of di-tert.-butyl dicarbonate were added to the dichloromethane layer and the mixture was stirred at room temperature overnight. The mixture was washed with 1 N sodium hydroxide, a mixture of 2N hydrochloric acid, brine and water (1:3:6) and brine, dried over sodium sulphate and evaporated to dryness. The crude product was purified by silica gel chromatography (heptanes: ethyl acetate) to give 1.22 g of the desired product. $R_t = 5.18$ min (Method 3). Detected mass: 815.4 ($2M+H^+$).

{1-[1-(4-Fluoro-phenyl)-4-oxo-cyclohexyl]-butyl}-carbamic acid tert-butyl ester (17)

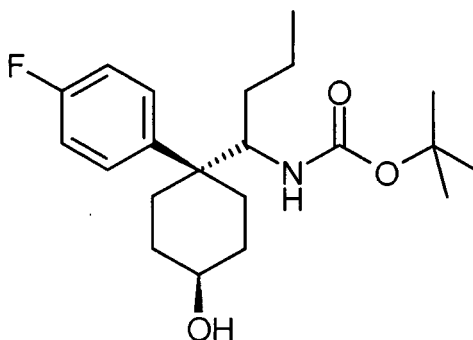
[0201]



[0202] 1.22 g of {1-[8-(4-fluoro-phenyl)-1,4-dioxo-spiro[4.5]dec-8-yl]-butyl}-carbamic acid tert-butyl ester (16) were dissolved in 42 mL of acetone and 3 mL of 1 N hydrochloric acid were added. The mixture was stirred at room temperature until conversion was complete. 40 mL of saturated aqueous sodium bicarbonate solution were added and the reaction mixture was extracted with ethyl acetate three times. The combined organic layer was extracted with brine, dried over sodium sulphate and evaporated to dryness to give 966 mg of crude (17), that was sufficiently pure for further conversion. $R_t = 1.72$ min (Method 5). Detected mass: 308.2 (M-Isobutene+H⁺).

trans-{1-[1-(4-Fluoro-phenyl)-4-hydroxy-cyclohexyl]-butyl}-carbamic acid tert-butyl ester (18)

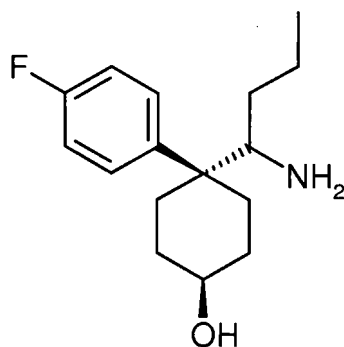
[0203]



[0204] 0.97 g of {1-[1-(4-Fluoro-phenyl)-4-oxo-cyclohexyl]-butyl}-carbamic acid tert-butyl ester (17) were dissolved in 14 mL of ethanol and 119 mg of sodium borohydride were added at -20°C. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was evaporated, the residue was dissolved in ethyl acetate and washed twice with 2N hydrochloric acid and once with brine. The organic layer was dried over sodium sulphate and evaporated to dryness to give the crude product, that was purified by silica gel chromatography (heptanes:ethyl acetate) to give 619 mg of (18). $R_t = 3.46$ min (Method 1). Detected mass: 366.3 (M+H⁺).

trans-4-(1-Amino-butyl)-4-(4-fluoro-phenyl)-cyclohexanol (19)

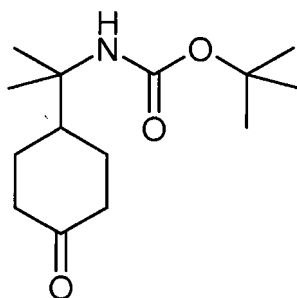
[0205]



[0206] 619 mg of trans-{1-(1-(4-Fluoro-phenyl)-4-hydroxy-cyclohexyl)-butyl}-carbamic acid tert-butyl ester (18) were dissolved in 2 mL of isopropanol and 2 mL of 2N aqueous hydrochloric acid were added. The mixture was stirred overnight. Water was added and the isopropanol was removed *in vacuo*. The residue was taken up in water and lyophilized for another two times to give 1.64 g of (19) as the hydrochloride.
 $R_t = 2.27$ min (Method 1). Detected mass: 266.2 ($M+H^+$).

[1-Methyl-1-(4-oxo-cyclohexyl)-ethyl]-carbamic acid tert-butyl ester (20)

[0207]



[0208] A suspension of commercial anhydrous cerium chloride (ABCR, 8.8 g) in anhydrous THF (62 mL) was heated for 4h at 60°C under vigorous stirring. The slurry was cooled to room temperature and treated with 3g of 4-cyanocyclohexanone cyclic ethylene acetal. After cooling to -20°C, 35 mL of a 1.5 M solution of MeLi LiBr in diethyl ether were added dropwise. The mixture was allowed to stir for 1 h at -10 °C, then 20 mL of THF were added and the reaction was quenched by addition of concentrated NH_4OH (10 mL) over 10 min. The mixture was allowed to warm to room temperature, stirred for 30 min, diluted with methyl tert. butyl ether and then filtered. The filter cake was rinsed several times with methyl tert. butyl ether. The combined filtrates were then concentrated *in vacuo*.

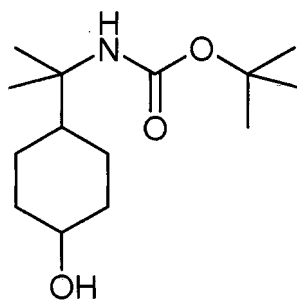
The crude product was dissolved in dichloromethane and extracted twice with 0.1 N HCl. The combined HCl layers were washed with dichloromethane, cooled and the pH was adjusted to 12 by addition of 5 N sodium hydroxide solution. The aqueous layer was extracted twice with dichloromethane. The dichloromethane layers were combined, washed with brine, and dried over sodium sulphate.

1.82 g of triethylamine and 2.74 g of di-tert.-butyl dicarbonate were added. The mixture was stirred for two days at room temperature, washed with 1 N sodium hydroxide solution, twice with 0.1 N hydrochloric acid and water, and once with brine, dried over sodium sulphate and evaporated to dryness to give 3.0 g of crude product.

The crude product was dissolved in 100 mL of acetone and 10 mL of 1 N HCl were added and stirred at room temperature. Additional HCl was added and stirring was continued until conversion was complete. Sodium hydroxide solution and methyl-tert.-butyl ether was added, the aqueous layer was separated and extracted with methyl-tert.-butyl ether. The combined ether layers were dried over sodium sulphate and evaporated to dryness to give 2.4 g of (20). $R_t = 3.08$ min (Method 1). Detected mass: 256.2 ($M+H^+$).

[1-Methyl-1-(4-hydroxy-cyclohexyl)-ethyl]-carbamic acid tert-butyl ester (21)

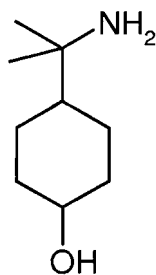
[0209]



[0210] 2.91 g of [1-Methyl-1-(4-oxo-cyclohexyl)-ethyl]-carbamic acid tert-butyl ester (20) were dissolved in 60 mL of ethanol and 473 mg of sodium borohydride were added at -20°C. The mixture was allowed to warm to room temperature and stirred for 3.5h. The mixture was evaporated, the residue was dissolved in ethyl acetate and washed twice with 2N hydrochloric acid and once with brine. The organic layer was dried over sodium sulphate and evaporated to dryness to give 2.74 g of (21). $R_t = 1.27$ min (Method 5). Detected mass: 194 (M-Isobutene- H_2O+H^+).

4-(1-Amino-1-methyl-ethyl)-cyclohexanol (22)

[0211]

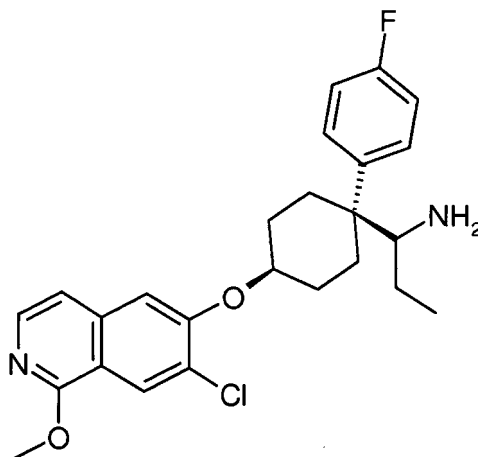


[0212] 580 mg of [1-Methyl-1-(4-hydroxy-cyclohexyl)-ethyl]-carbamic acid tert-butyl ester (21) were dissolved in 10 mL of isopropanol and 10 mL of 2N hydrochloric acid were added. The mixture was stirred overnight. Water was added and the isopropanol was removed *in vacuo*. The residue was taken up in water and lyophilized for another two times from water to give 515 mg of (22) as the hydrochloride. $R_t = 0.18$ min (Method 5). Detected mass: 158.2 (M+ H^+).

Example 1: cis-6-[4-(1-Amino-propyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one

a) cis-1-[4-(7-Chloro-1-methoxy-isoquinolin-6-yloxy)-1-(4-fluoro-phenyl)-cyclohexyl]-propylamine (23)

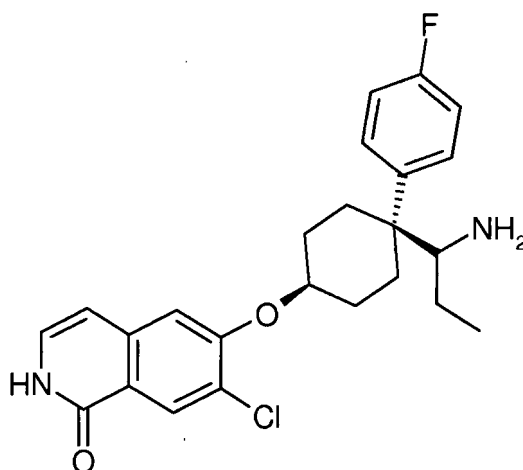
[0213]



[0214] 1.7 g of cis-4-(1-Amino-propyl)-4-(4-fluoro-phenyl)-cyclohexanol (14) were dissolved under argon in 50 mL of dry dimethyl acetamide. 513 mg of sodium hydride (95%) were added portionwise under cooling and the mixture was allowed to stir for 10 minutes. 1.57 g of 7-Chloro-6-fluoro-1-methoxy-isoquinoline (10) were added and the mixture was heated at 50 °C for 3h. Stirring was continued overnight at room temperature. The reaction mixture was cooled in an ice bath and 50 mL of water were added carefully. The mixture was extracted four times with dichloromethane:isopropanol (3:1) and the combined organic layer was washed three times with water and once with brine, dried over sodium sulphate and evaporated to dryness. Water was added and the mixture was lyophilized. The crude product was subjected to silica gel chromatography (dichloromethane:methanol) to give 1.66 g of the desired product. $R_t = 3.45$ min (Method 1). Detected mass: 443.2 (M+H⁺).

b) cis-6-[4-(1-Amino-propyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one (Example 1)

[0215]

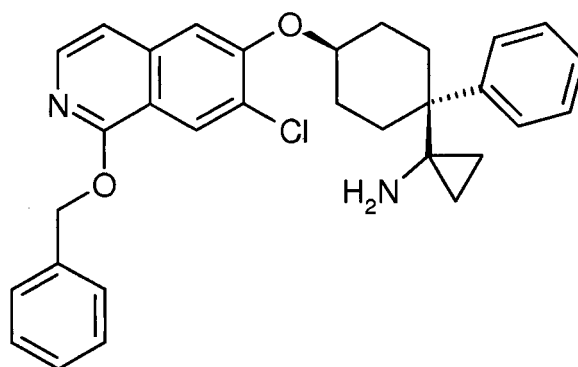


[0216] 1.66 g of cis-1-[4-(7-Chloro-1-methoxy-isoquinolin-6-yloxy)-1-(4-fluoro-phenyl)-cyclohexyl]-propylamine (23) were dissolved in 16 mL of a mixture of isopropanol and 1 N hydrochloric acid (1:1) and heated in a microwave oven for 20 minutes at 120°C. Water was added, the isopropanol removed *in vacuo* and the remaining solution was lyophilized. The residue was taken up in water and lyophilized for another two times from water to give 1.64 g of the desired product Example 1 as the hydrochloride. $R_t = 2.67$ min (Method 1). Detected mass: 429.2 (M+H⁺).

Example 2: cis-6-[4-(1-Amino-cyclopropyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one

a) cis-1-[4-(1-Benzyloxy-7-chloro-isoquinolin-6-yloxy)-1-phenyl-cyclohexyl]-cyclopropylamine (24)

[0217]

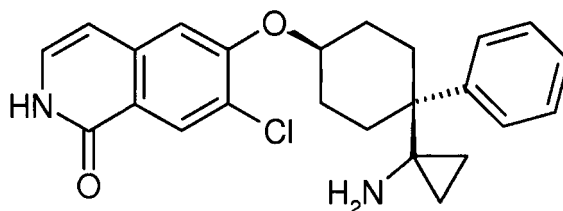


[0218] To a solution of dry cis-4-(1-aminocyclopropyl)-4-phenylcyclohexanol (4, 0.2 g, 0.75 mmol) in anhydrous *N,N*-dimethylacetamide (5 mL) at 0°C was added portionwise sodium hydride (60% in mineral oil, 0.12 g, 3 mmol). The reaction mixture was stirred for 10 min at room temperature, 1-(benzyloxy)-7-chloro-6-fluoroisoquinoline (38, 0.28 g,

0.97 mmol) was then added and stirring was continued overnight. The suspension was poured onto ice, the resulting precipitate was filtered and dried. The crude product was purified by chromatography on silica gel (eluting with 0 to 5 % methanol in dichloromethane containing 1% ammonia) to yield 0.252 g of the desired product. $R_t = 6.21$ min (Method 9). Detected mass: 499 ($M+H^+$).

b) cis-6-[4-(1-Amino-cyclopropyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one (Example 2)

[0219]

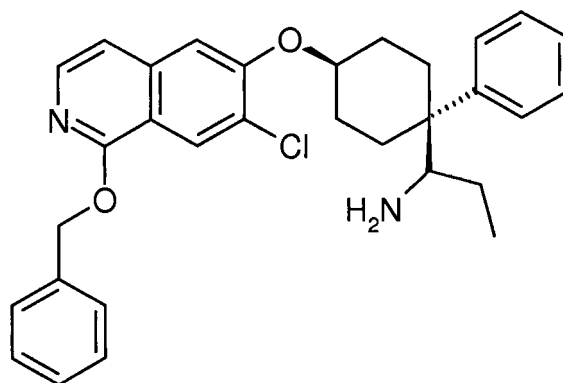


[0220] To a solution of cis-1-[4-[[7-chloro-1-(phenylmethoxy)-6-isoquinolinyl]oxy]-1-phenylcyclohexyl]-cyclopropanamine (24, 0.24 g, 0.48 mmol) in isopropanol (2.5 mL) was added a solution of 4N aqueous hydrochloric acid (2.5 mL, 10 mmol) followed by 2.5 mL of isopropanol, 2.5 mL of 4N aqueous hydrochloric acid (10 mmol) and eventually 2.5 mL of methanol. The resulting suspension was stirred overnight, evaporated under reduced pressure and co-evaporated with a methanol/toluene mixture. The crude product was triturated with methanol/diethyl ether to afford 0.18 g of the title compound as its hydrochloride. $R_t = 4.83$ min (Method 9). Detected mass: 409 ($M+H^+$).

Example 3: cis-6-[[4-(1-aminopropyl)-4-phenylcyclohexyl]oxy]-7-chloro-2H-isoquinolin-1-one

a) cis-1-(4-[[1-(benzyloxy)-7-chloroisoquinolin-6-yl]oxyl-phenylcyclohexyl]-propanamine (25)

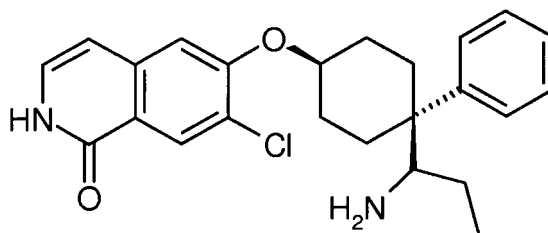
[0221]



[0222] To a solution of cis-4-(1-aminopropyl)-4-phenylcyclohexanol (6, 0.39 g, 1.48 mmol) in anhydrous N,N-dimethylacetamide (10 mL) was added portionwise sodium hydride (60% in mineral oil, 0.24 g, 5.92 mmol). The reaction mixture was stirred for 10 min at room temperature, then 1-(benzyloxy)-7-chloro-6-fluoroisoquinoline (38, 0.42 g, 1.48 mmol) was added and stirring was continued for 72 hours. The suspension was poured onto ice, the resulting aqueous layer was extracted with chloroform. The organic layers were dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (eluting with 0 to 10 % methanol in dichloromethane) to yield 0.604 g of cis-1-(4-[[1-(benzyloxy)-7-chloroisoquinolin-6-yl]oxy]-1-phenylcyclohexyl)propanamine (25). $R_t = 4.18$ min (Method 8). Detected mass: 501 ($M+H^+$).

b) cis-6-[[4-(1-aminopropyl)-4-phenylcyclohexyl]oxy]-7-chloro-2H-isoquinolin-1-one (Example 3)

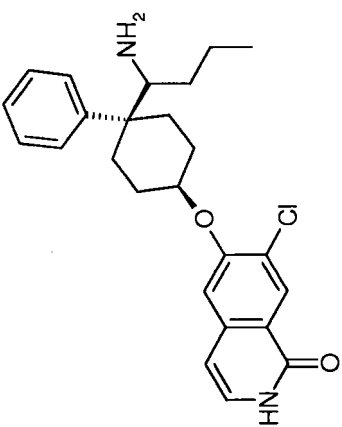
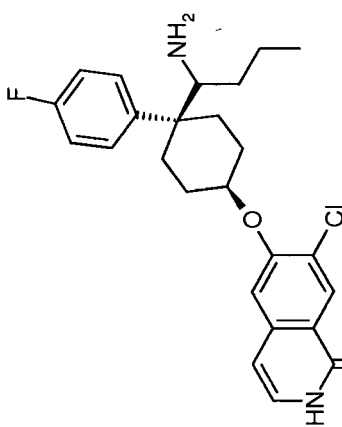
[0223]



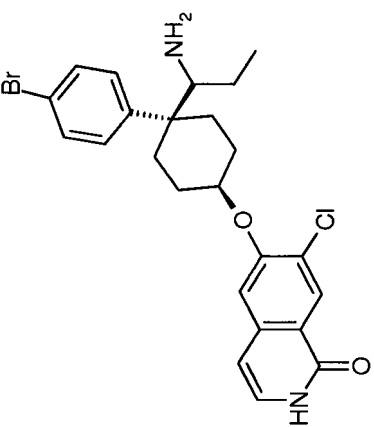
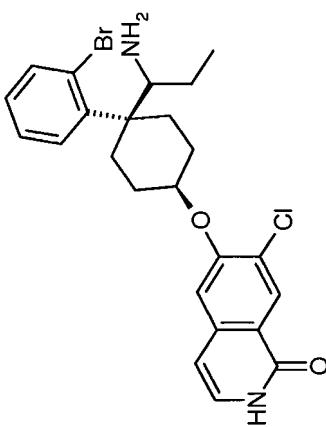
[0224] To a solution of cis-1-(4-[[1-(benzyloxy)-7-chloroisoquinolin-6-yl]oxy]-1-phenylcyclohexyl)propanamine (25, 0.604 g, 1.21 mmol) in isopropanol (6.3 mL) was added a solution of 1 N aqueous hydrochloric acid (7 mL, 7 mmol). The resulting suspension was stirred overnight and evaporated under reduced pressure. The crude product was purified by reversed phase column chromatography (eluting with 0 to 30% CH₃CN in water) to afford the title compound (0.32 g). R_t = 5.00 min (Method 9). Detected mass: 411 (M+H⁺).

[0225] The following examples were prepared in a similar fashion as described for Example 1, starting from a suitably protected isoquinolinone and the respective aminoalcohol.

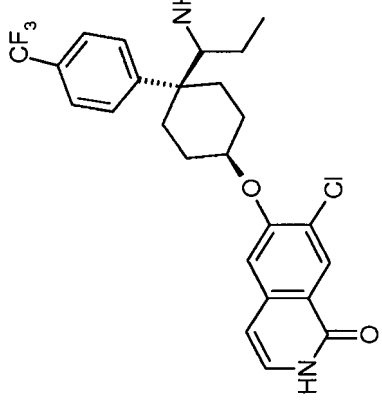
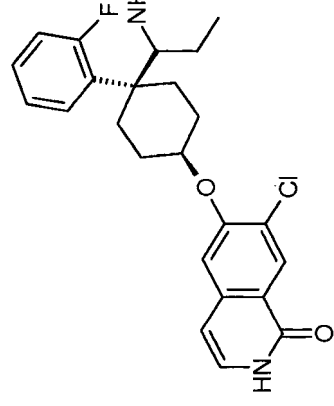
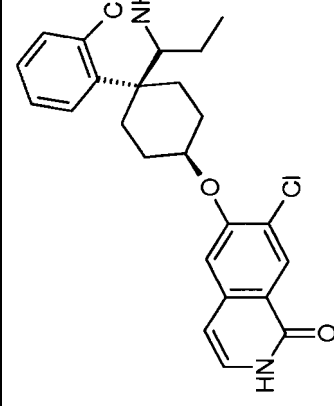
[0226] Aminoalcohols were synthesized from the corresponding benzonitriles and grignard reagents: trans-aminoalcohols were obtained in a similar fashion as described in the reaction sequence to yield (19), cis-aminoalcohols were obtained in a similar fashion as described in the reaction sequence to yield (14). Dimethylated aminoalcohols were obtained in a similar fashion as described for (22). All described products were obtained as the hydrochloride salts.

Ex. No.	Isoquinoline	Product	Chemical Name	[M+H ⁺]	R _t [min]	Method
4	10		cis-6-[4-(1-Amino-butyl)-4-phenyl-cyclo hexyloxy]-7-chloro-2H-isoquinolin-1-one	425.2	2.61	1
5	10		cis-6-[4-(1-Amino-butyl)-4-(4-fluorophenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	443.2	2.66	1

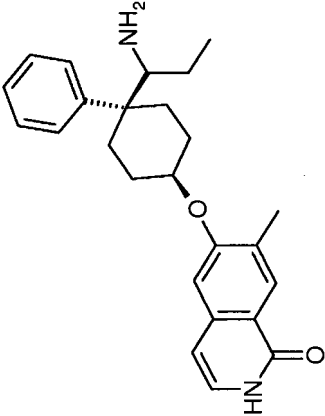
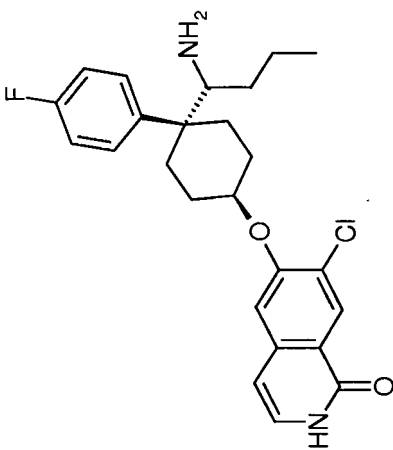
(continued)

Ex. No.	Isoquinoline	Product	Chemical Name	[M+H ⁺]	R _f [min]	Method
6	10		cis-6-[4-(1-Amino-propyl)-4-(4-bromo-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	489.1	2.69	1
7	10		cis-6-[4-(1-Amino-propyl)-4-(2-bromo-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	489.1	2.64	1

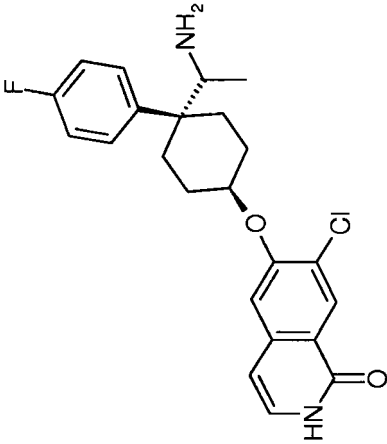
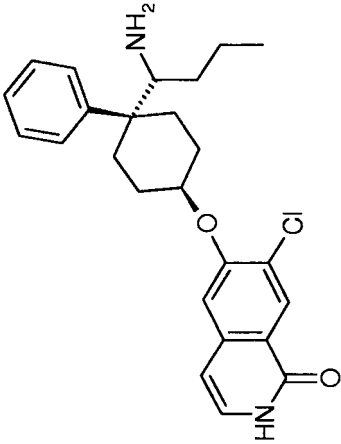
(continued)

Ex. No.	Isoquinoline	Product	Chemical Name	[M+H ⁺]	R _f [min]	Method
8	10		cis-6-[4-(1-Amino-propyl)-4-(4-trifluoro methyl-phenyl)-cyclo-hexyloxy]-7-chloro-2H-isoquinolin-1-one	479.2	2.74	1
9	10		cis-6-[4-(1-Amino-propyl)-4-(2-fluorophenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	429.2	2.52	1
10	10		cis-6-[4-(1-Amino-propyl)-4-(2-chloro-phenyl)-cyclohexyloxy]-7-chloro-2H-iso quinolin-1-one	445.1	2.71	1

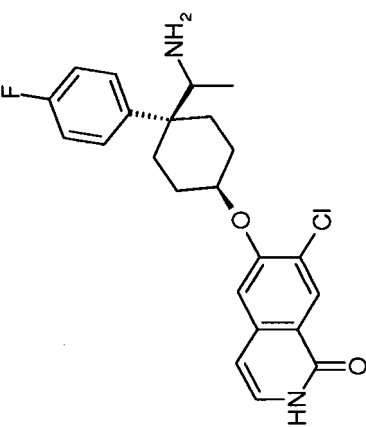
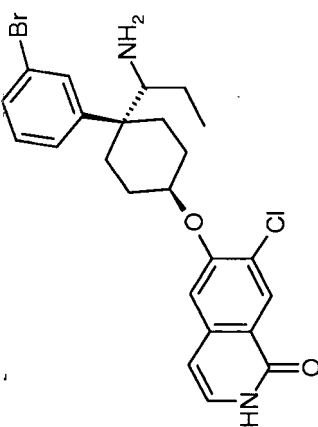
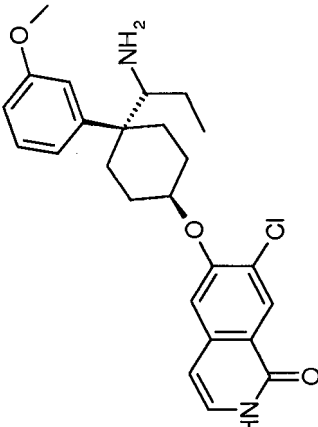
(continued)

Ex. No.	Isoquinoline	Product	Chemical Name	[M+H ⁺]	R _f [min]	Method
11	39		cis-6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-methyl-2H-iso quinolin-1-one	391.2	2.56	1
12	38		trans-6-[4-(1-Amino-butyl)-4-(4-fluorophenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	443.2	2.63	1

(continued)

Ex. No.	Isoquinoline	Product	Chemical Name	[M+H ⁺]	R _f [min]	Method
13	38		trans-6-[4-(1-Amino-ethyl)-4-(4-fluorophenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	415.2	2.48	1
14	38		trans-6-[4-(1-Amino-butyl)-4-phenylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	425.2	2.67	1

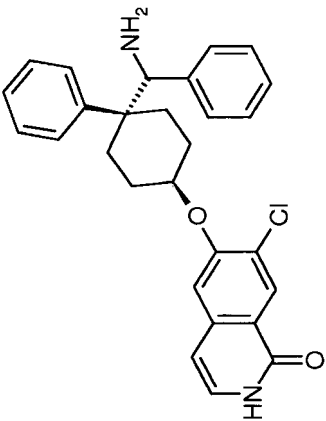
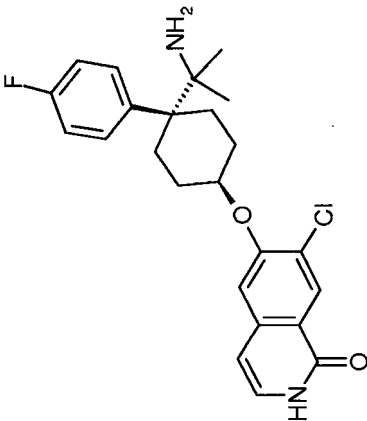
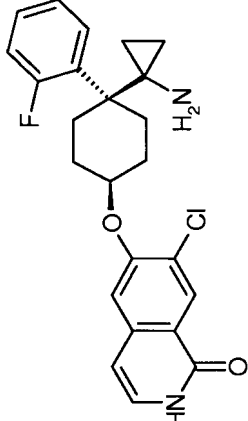
(continued)

Ex. No.	Isoquinoline	Product	Chemical Name	[M+H ⁺]	R _f [min]	Method
15	38		cis-6-[4-(1-Amino-ethyl)-4-(4-fluorophenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	415.2	2.48	1
16	10		trans-6-[4-(1-Amino-propyl)-4-(3-bromo-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	489.2	2.77	2
17	10		trans-6-[4-(1-Amino-propyl)-4-(3-methoxyphenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	441.2	2.65	2

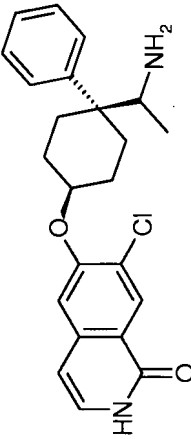
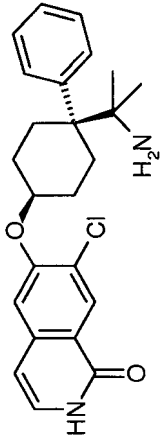
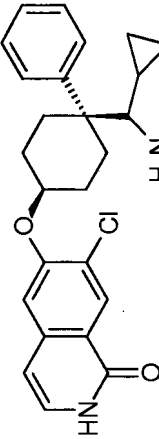
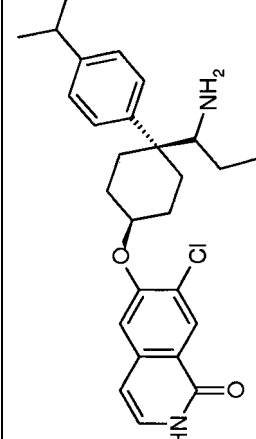
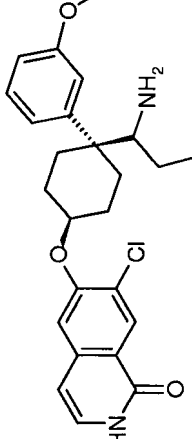
(continued)

Ex. No.	Isoquinoline	Product	Chemical Name	[M+H ⁺]	R _f [min]	Method
18	10		trans-6-[4-(Amino-phenyl(methyl))-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	477.2	2.67	1
19	10		trans-6-[4-(1-Amino-2-methylpropyl)-4-phenylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	425.3	3.33	6
20	10		trans-6-[4-(1-Amino-3-methylbutyl)-4-phenylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	439.4	2.74	1

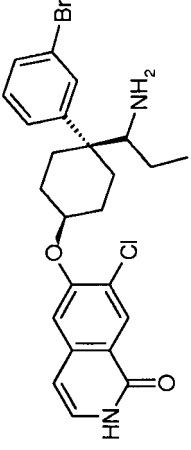
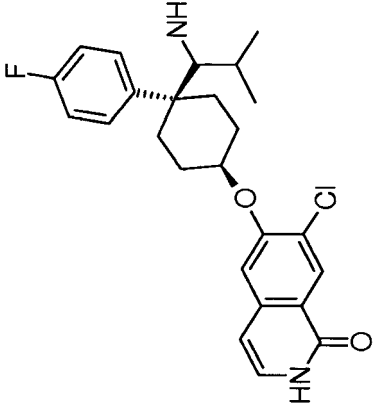
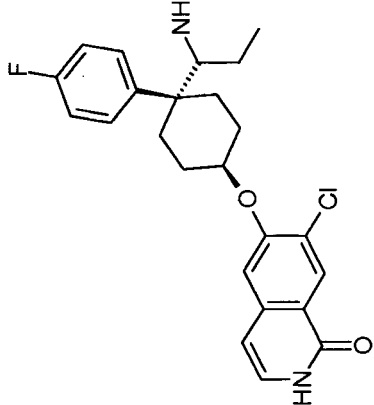
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Ex. No.	Isoquinoline	Product	Chemical Name	[M+H ⁺]	R _f [min]	Method
21	10		trans-6-[4-(Amino-phenylmethyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	458.2	2.78	1
22	38		trans-6-[4-(1-Amino-1-methylethyl)-4-(4-fluorophenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	429.1	2.64	1
23	38		cis-6-[4-(1-Amino-cyclopropyl)-4-(2-fluorophenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	427	3.29	8

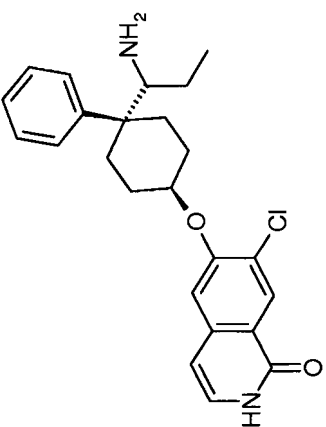
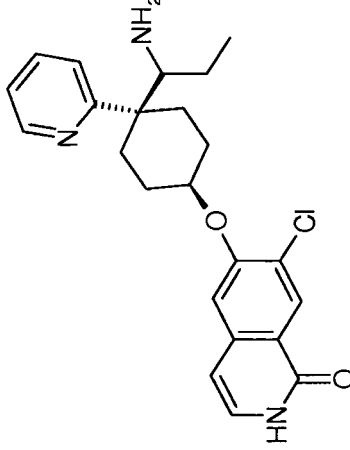
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Ex. No.	Isoquinoline	Product	Chemical Name	[M+H ⁺]	R _f [min]	Method
24	38		cis-6-[4-(1-Amino-ethyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	397	3.19	8
25	38		cis-6-[4-(1-Amino-1-methyl-ethyl)-4-phenyl-cyclo-hexyloxy]-7-chloro-2H-isoquinolin-1-one	411	0.62	7
26	38		cis-6-[4-[amino (cyclopropyl) methyl]-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	423	5.10	9
27	10		cis-6-[4-(1-Amino-propyl)-4-(4-isopropylphenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	453.2	1.20	5
28	10		cis-6-[4-(1-Amino-propyl)-4-(3-methoxy-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	441.2	1.07	5

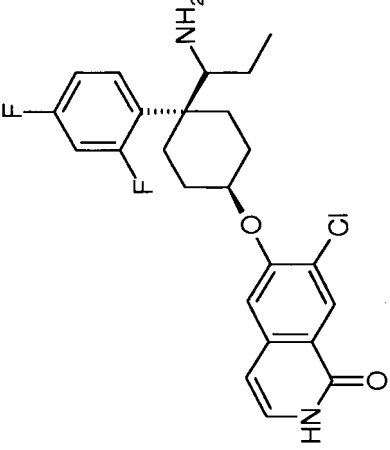
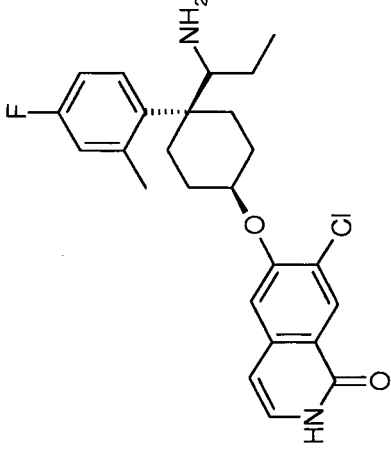
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Ex. No.	Isoquinoline	Product	Chemical Name	[M+H ⁺]	R _f [min]	Method
29	10		cis-6-[4-(1-Amino-propyl)-4-(3-bromo-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	503.1	1.34	5
30	10		cis-6-[4-(1-Amino-2-methyl-propyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	443.2	2.66	1
31	10		trans-6-[4-(1-amino-propyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	429.2	2.57	1

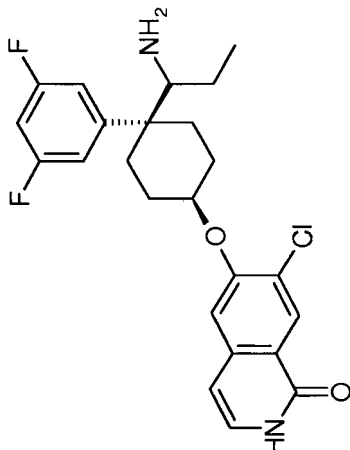
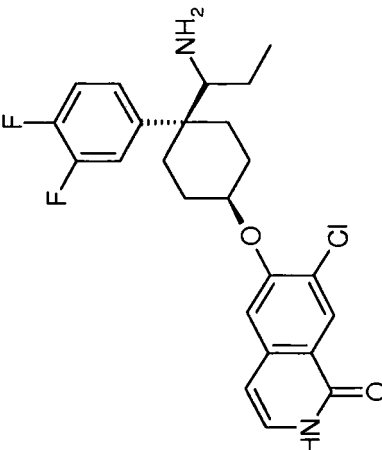
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Ex. No.	Isoquinoline	Product	Chemical Name	[M+H ⁺]	R _f [min]	Method
32	38		trans-6-[4-(1-amino-propyl)-4-phenyl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	411.2	2.69	1
55	10		cis-6-[4-(1-Amino-propyl)-4-pyridin-2-yl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	412.2	1.77	13

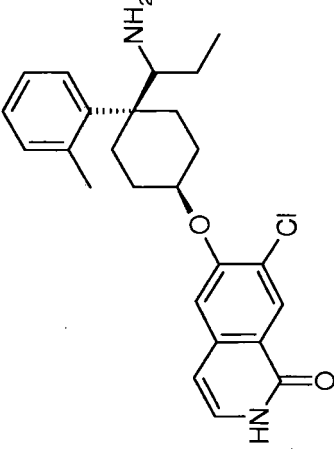
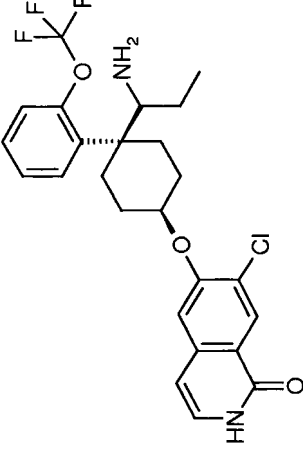
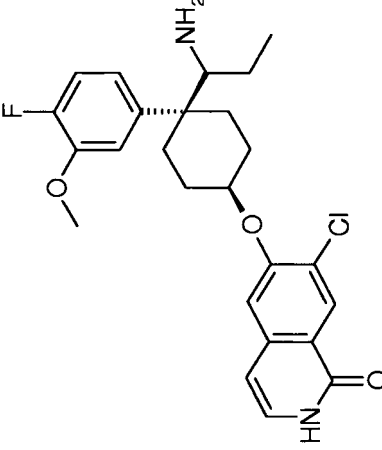
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Ex. No.	Isoquinoline	Product	Chemical Name	[M+H ⁺]	R _V [min]	Method
56	10		cis-6-[4-(1-Amino-propyl)-4-(2,4-difluorophenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	447.1	1.84	12
57	10		cis-6-[4-(1-Amino-propyl)-4-(4-fluoro-2-methyl-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	443.1	1.89	12

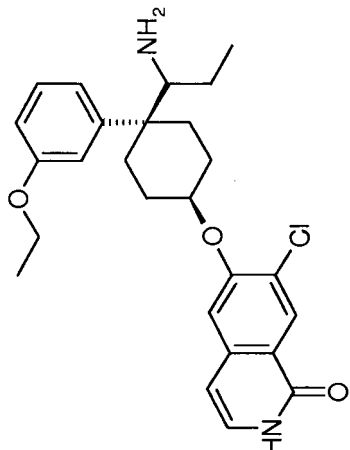
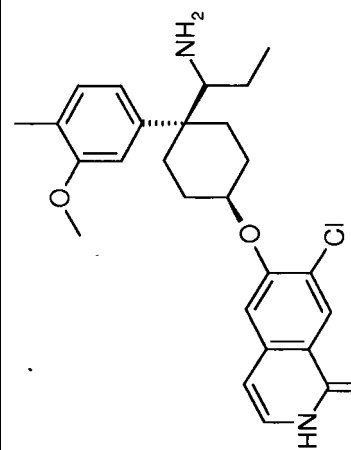
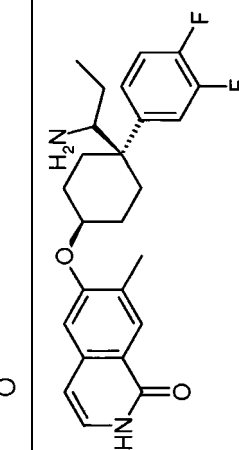
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Ex. No.	Isoquinoline	Product	Chemical Name	[M+H ⁺]	R _t [min]	Method
58	10		cis-6-[4-(1-Amino-propyl)-4-(3,5-difluorophenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	447.1	1.86	12
59	10		cis-6-[4-(1-Amino-propyl)-4-(3,4-difluorophenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	447.1	1.87	12

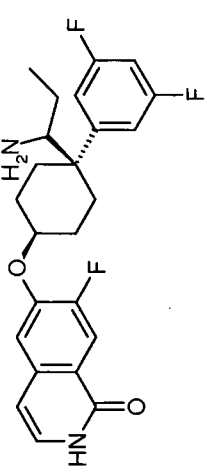
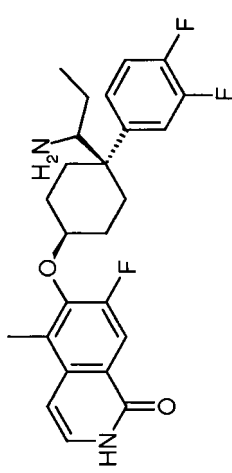
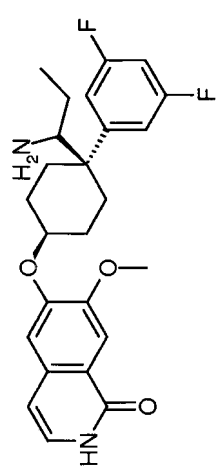
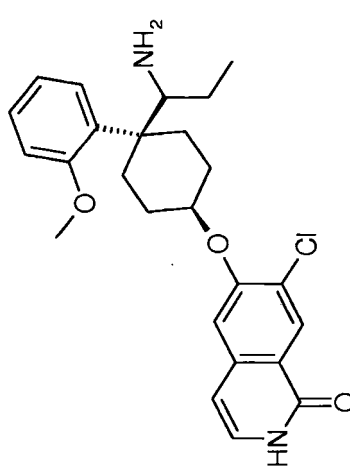
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Ex. No.	Isoquinoline	Product	Chemical Name	[M+H ⁺]	R _f [min]	Method
60	10		cis-6-[4-(1-Amino-propyl)-4-o-tolyl(cyclohexyloxy)]-7-chloro-2H-isoquinolin-1-one	425.1	1.82	12
61	10		cis-6-[4-(1-Amino-propyl)-4-(2-trifluoro methoxy-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	495.2	1.97	12
62	10		cis-6-[4-(1-Amino-propyl)-4-(4-fluoro-3-methoxyphenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	459.3	1.28	16

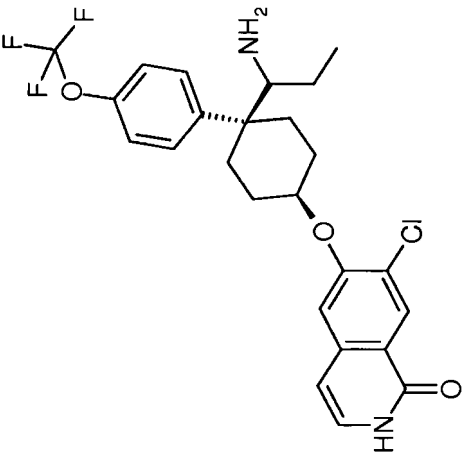
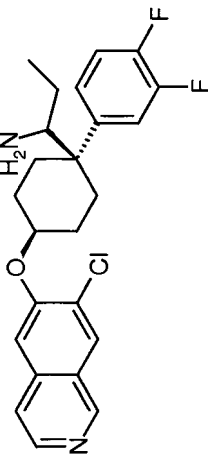
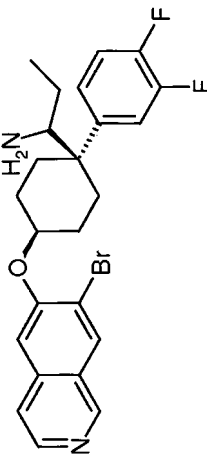
(continued)

Ex. No.	Isoquinoline	Product	Chemical Name	[M+H ⁺]	R _f [min]	Method
63	10		cis-6-[4-(1-Amino-propyl)-4-(3-ethoxy-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	455.3	1.24	16
64	10		cis-6-[4-(1-Amino-propyl)-4-(3-methoxy-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	438.2 (M+H ⁺ -NH ₃)	3.69	3
65	52		cis-6-[4-(1-Amino-propyl)-4-(3,4-difluorophenyl)-cyclohexyloxy]-7-methyl-2H-isoquinolin-1-one	427.2	1.38	10

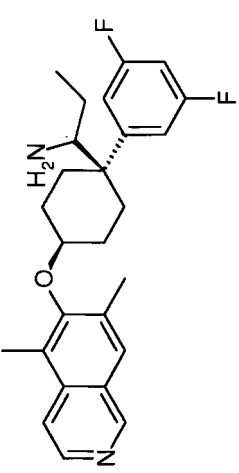
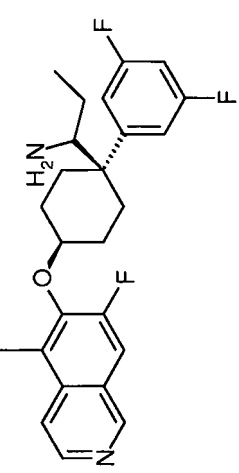
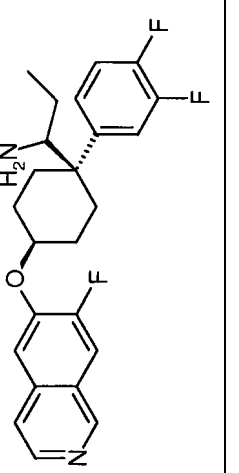
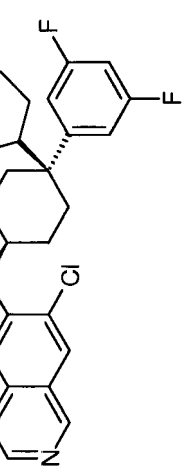
(continued)

Ex. No.	Isoquinoline	Product	Chemical Name	[M+H ⁺]	R _f [min]	Method
66	50		cis-6-[4-(1-Amino-propyl)-4-(3,5-difluorophenyl)-cyclohexyloxy]-7-fluoro-2H-isoquinolin-1-one	431.2	1.36	10
67	51		cis-6-[4-(1-Amino-propyl)-4-(3,4-difluorophenyl)-cyclohexyloxy]-7-fluoro-5-methyl-2H-isoquinolin-1-one	445.3	0.98	11
68	54		cis-6-[4-(1-Amino-propyl)-4-(3,5-difluorophenyl)-cyclohexyloxy]-7-methoxy-2H-isoquinolin-1-one	443.3	0.96	11
69	10		cis-6-[4-(1-Amino-propyl)-4-(2-methoxyphenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	441.2	1.88	13

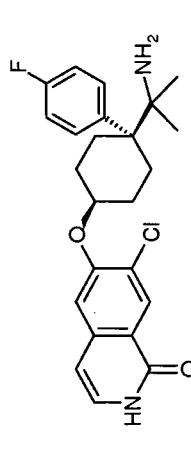
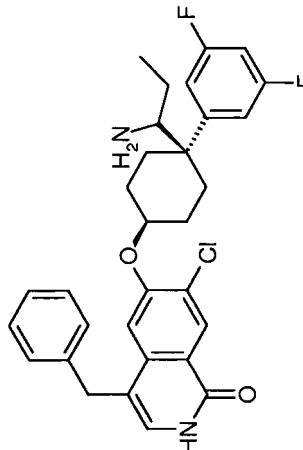
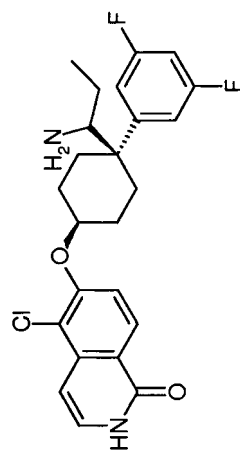
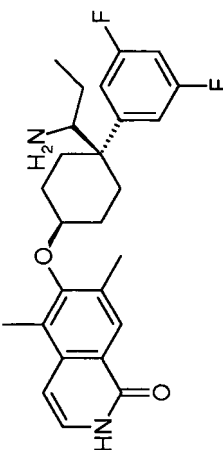
(continued)

Ex. No.	Isoquinoline	Product	Chemical Name	[M+H] ⁺	R _t [min]	Method
70	10		cis-6-[4-(1-Amino-propyl)-4-(4-trifluoromethoxyphenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	495.2	2.32	14
71	7-Chloro -6-fluoro-isoquinoline		cis-1-[4-(7-Chloro-isoquinolin-6-yloxy)-1-(3,4-difluorophenyl)-cyclohexyl]-propylamine	431.3	2.28	2
72	46		cis-1-[4-(7-Bromo-iso quinolin-6-yloxy)-1-(3,4-difluorophenyl)-cyclohexyl]-propylamine	475.3	2.34	2

(continued)

Ex. No.	Isoquinoline	Product	Chemical Name	[M+H ⁺]	R _f [min]	Method
73	44		cis-1-[1-(3,5-Difluoro-phenyl)-4-(5,7-dimethyl-isoquinolin-6-yloxy)-cyclohexyl]-propylamine	425.3	0.87	11
74	43		cis-1-[1-(3,5-Difluoro-phenyl)-4-(7-fluoro-5-methyl-isoquinolin-6-yloxy)-cyclohexyl]-propylamine	429.3	1.30	10
75	45		cis-1-[1-(3,4-Difluoro-phenyl)-4-(7-fluoro-isoquinolin-6-yloxy)-cyclohexyl]-propylamine	415.3	2.24	2
76	7-Chloro-6-fluoro-isoquinoline		cis-1-[4-(7-Chloro-isoquinolin-6-yloxy)-1-(3,5-difluoro-phenyl)-cyclohexyl]-propylamine	431.1	1.20	10

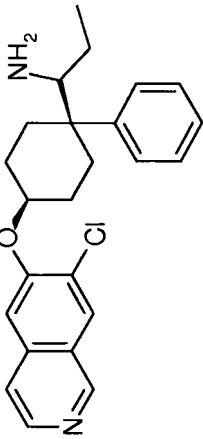
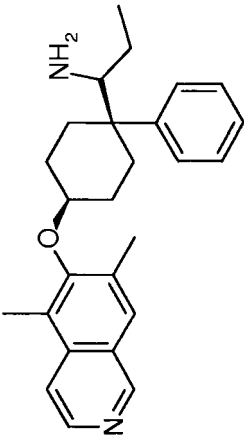
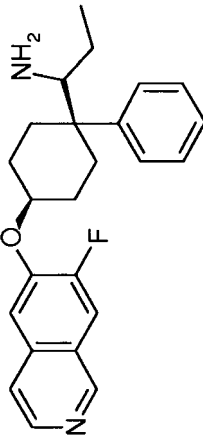
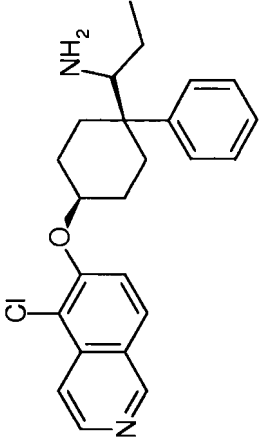
(continued)

Ex. No.	Isoquinoline	Product	Chemical Name	[M+H ⁺]	R _f [min]	Method
77	10		cis-6-[4-(1-Amino-1-methyl-ethyl)-4-(4-fluorophenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	431.3	0.70	15
78	55		cis-6-[4-(1-Amino-propyl)-4-(3,5-difluorophenyl)-cyclohexyloxy]-4-benzyl-7-chloro-2H-isoquinolin-1-one	537.2	1.50	10
79	49		cis-6-[4-(1-Amino-propyl)-4-(3,5-difluorophenyl)-cyclohexyloxy]-5-chloro-2H-isoquinolin-1-one	447.2	1.33	10
80	53		cis-6-[4-(1-Amino-propyl)-4-(3,5-difluorophenyl)-cyclohexyloxy]-5,7-dimethyl-2H-isoquinolin-1-one	441.3	3.24	6

(continued)

Ex. No.	Isoquinoline	Product	Chemical Name	[M+H ⁺]	R _f [min]	Method
85	52		cis-6-[4-(1-Amino-propyl)-4-(3-trifluoromethoxy-phenyl)-cyclohexyloxy]-7-methyl-2H-iso quinolin-1-one	475.3	1.36	16
86	52		cis-6-[4-(1-Amino-propyl)-4-(3-trifluoro methyl-phenyl)-cyclohexyloxy]-7-methyl-2H-isoquinolin-1-one	459.2	1.32	16
87	50		cis-6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-fluoro-2H-iso quinolin-1-one	395.2	1.37	10
88	51		cis-6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-fluoro-5-methyl-2H-isoquinolin-1-one	409.3	0.96	11

(continued)

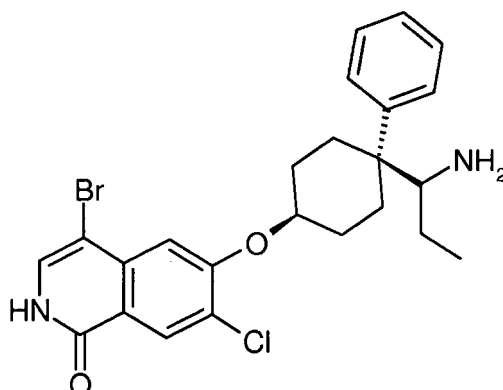
Ex. No.	Isoquinoline	Product	Chemical Name	[M+H ⁺]	R _f [min]	Method
89	7-chloro-6-fluoro-isoquinoline		cis-1-[4-(7-Chloro-isoquinolin-6-yloxy)-1-phenylcyclohexyl]-propylamine	395.2	1.20	10
90	44		cis-1-[4-(5,7-Dimethyl-isoquinolin-6-yloxy)-1-phenylcyclohexyl]-propylamine	389.3	0.86	11
91	45		cis-1-[4-(7-Fluoro-isoquinolin-6-yloxy)-1-phenylcyclohexyl]-propylamine	379.2	1.16	10
92	5-chloro-6-fluoro-isoquinoline		cis-1-[4-(5-Chloro-isoquinolin-6-yloxy)-1-phenylcyclohexyl]-propylamine	395.2	1.18	10

(continued)

Ex. No.	Isoquinoline	Product	Chemical Name	[M+H ⁺]	R _f [min]	Method
93	43		cis-1-[4-(7-Fluoro-5-methyl-isoquinolin-6-yloxy)-1-phenylcyclohexyl]-propylamine	393.2	1.20	10
94	46		cis-1-[4-(7-Bromo-isoquinolin-6-yloxy)-1-phenylcyclohexyl]-propylamine	439.1	1.19	10
95	48		cis-1-[4-(7-Methyl-isoquinolin-6-yloxy)-1-phenylcyclohexyl]-propylamine	375.3	1.22	10
96	55		cis-6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-4-benzyl-7-chloro-2H-isoquinolin-1-one	501.3	1.50	10

Example 33: cis-6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-4-bromo-7-chloro-2H-isoquinolin-1-one

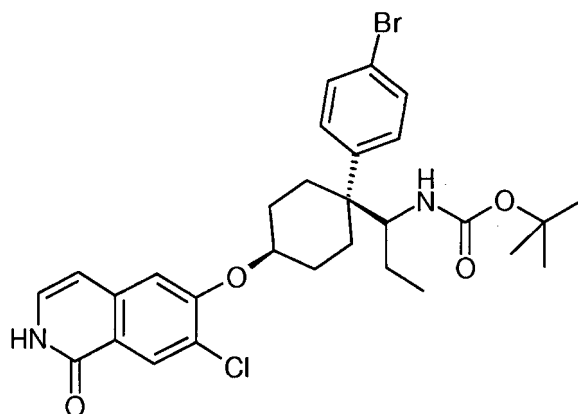
[0227]



[0228] 100 mg of Example 3 were dissolved in 3 mL of chloroform. 100 μ L of triethylamine and 268 μ L of a 1 M solution of bromine in chloroform were added. The reaction was stirred at room temperature until conversion was complete. The mixture was quenched by addition of 11 mL sat. sodium thiosulfate solution. 5 mL of 2N sodium hydroxide solution were added and the aqueous layer was extracted three times with dichloromethane:isopropanol (3:1). The combined organic layer was washed with 2N NaOH and brine, dried over sodium sulphate and evaporated. The mixture was purified by HPLC and the obtained product was dissolved in 1 mL of isopropanol:1N HCl and heated in a microwave oven for 20 minutes at 100°C. The mixture was evaporated to dryness, taken up in water and lyophilized to give 29 mg of the desired product as the hydrochloride. R_t = 2.77 min (Method 1). Detected mass: 491.1 (M+H⁺).

cis-{1-[1-(4-Bromo-phenyl)-4-(7-chloro-1-oxo-1,2-dihydro-isoquinolin-6-yloxy)-cyclohexyl]-propyl}-carbamic acid tert-butyl ester (81)

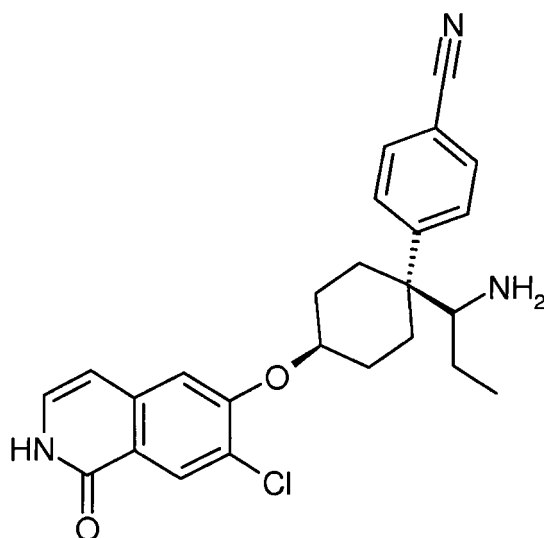
[0229]



[0230] 1.11 g of Example 6 were dissolved in 100 mL of dry dichloromethane. 1.2 mL of triethylamine and 1.44 g of di-tert.butyl dicarbonate were added. After conversion was complete, the mixture was extracted with 1 N sodium hydroxide solution, 0.2 N hydrochloric acid, water and brine, dried and evaporated. The crude product was purified by silica gel filtration to give 886 mg of the desired product. R_t = 4.00 min (Method 1). Detected mass : 533.0 (M+H-isobutene⁺).

Example 97: cis-4-[1-(1-Amino-propyl)-4-(7-chloro-1-oxo-1,2-dihydro-isoquinolin-6-yloxy)-cyclohexyl]-benzonitrile

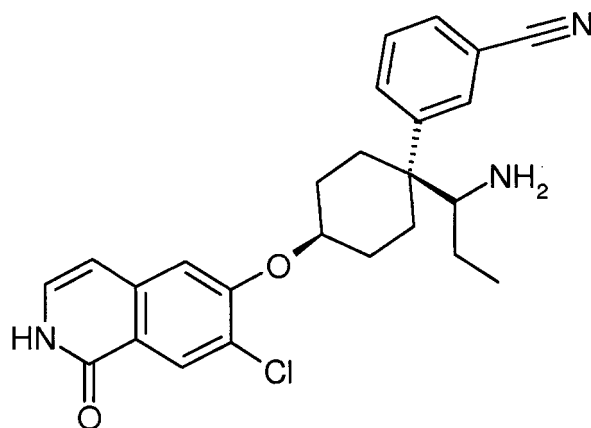
[0231]



[0232] 200 mg of 81 were dissolved in 10 mL of degassed dimethyl formamide and 50 mg of zinc cyanide and 18 mg of tetrakis(triphenylphosphine)palladium(0) were added under argon. The mixture was heated in a microwave oven for 30 minutes at 150°C. The mixture was diluted with methyl tert. butyl ether and filtered over Celite. The organic layer was washed twice with water and once with brine, dried over sodium sulphate and evaporated to dryness. The crude product was purified by silica gel chromatography and subsequently taken up in 2 mL of isopropanol and 2 mL of 1 N hydrochloric acid and heated in a microwave oven at 100°C for 1 hour. Water was added and the mixture was lyophilized. The residue was taken up in water and lyophilized again to give 65 mg of the desired product as hydrochloride. $R_t = 2.55$ min (Method 2). Detected mass: 436.2 ($M+H^+$).

Example 98: cis-3-[1-(1-Amino-propyl)-4-(7-chloro-1-oxo-1,2-dihydro-isoquinolin-6-yloxy)-cyclohexyl]benzonitrile

[0233]

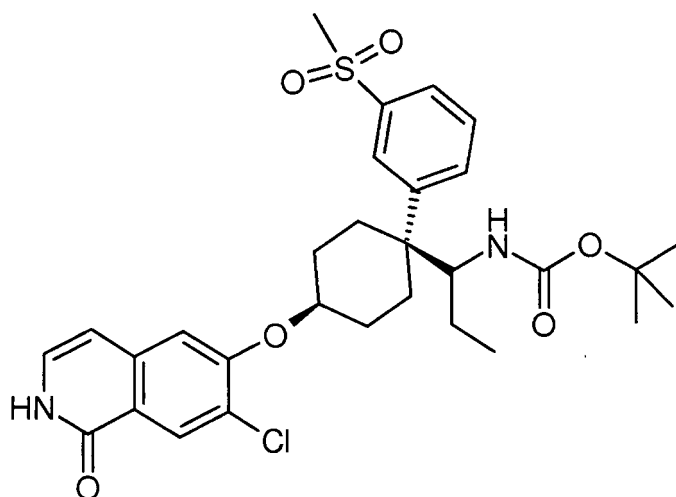


[0234] Example 98 can be obtained following a similar reaction sequence as used for the synthesis of Example 97, starting from Example 16. $R_t = 2.98$ min (Method 3). Detected mass: 436.2 ($M+H^+$).

Example 99: 6-[cis-4-(1-Amino-propyl)-4-(3-methanesulfonyl-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one

a) cis-{1-[4-(7-Chloro-1-oxo-1,2-dihydro-isoquinolin-6-yloxy)-1-(3-methanesulfonylphenyl)-cyclohexyl]-propyl-carbamic acid tert-butyl ester (82)}

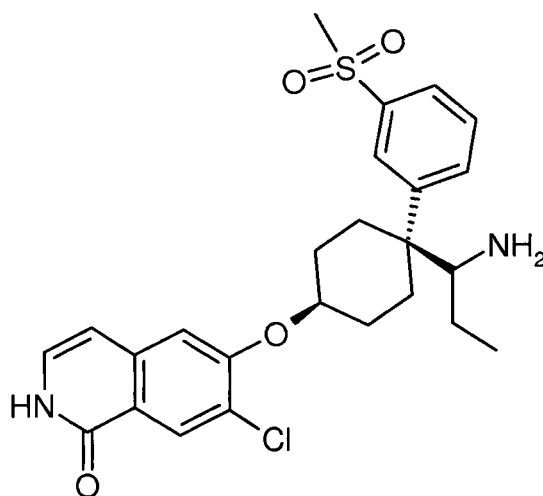
[0235]



[0236] 330 mg (559 μ mol) of cis-1-[1-(3-Bromo-phenyl)-4-(7-chloro-1-oxo-1,2-dihydroisoquinolin-6-yloxy)-cyclohexyl]-propyl-carbamic acid tert-butyl ester (obtained from Example 29 as described for synthesis of 81), 213 mg (1.1 mmol) CuI and 114 mg (1.1 mmol) methanesulfinic acid sodium salt were dissolved in 10 mL of anhydrous NMP. The mixture was stirred at 150 °C for 1 h under microwave irradiation, then poured into 100 mL of a saturated aqueous NaHCO₃-solution and extracted three times using 30 mL of ethyl acetate each. The organic layer was then washed five times using 20 mL of water each, dried over MgSO₄, filtered and the solvent removed under reduced pressure. Flash chromatography using ethyl acetate yielded 143 mg of 82 as a viscous oil. R_f (ethyl acetate): 0.33

b) Example 99: cis-6-[4-(1-Amino-propyl)-4-(3-methanesulfonyl-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one

[0237]

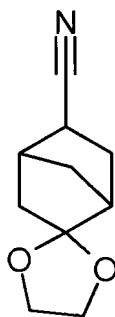


[0238] 140 mg (238 μ mol) of cis-1-[4-(7-Chloro-1-oxo-1,2-dihydro-isoquinolin-6-yloxy)-1-(3-methanesulfonyl-phenyl)-cyclohexyl]-propyl-carbamic acid tert-butyl ester (82) were dissolved in 3 mL of isopropanol and 3 mL of a 2N aqueous solution of HCl added. The mixture was stirred for 20h at ambient temperature, diluted with 30 mL of water and freeze dried to yield 120 mg of Example 99 as its hydrochloride as an amorphous solid. R_t = 0.66 min (Method 18). Detected mass: 489.2 (M+H⁺)

Example 100: 6-[(1S,4S,5S)-5-(1-Amino-propyl)-5-phenyl-bicyclo[2.2.1]hept-2-yloxy]-7-chloro-2H-isoquinolin-1-one

a) 5-Oxo-bicyclo[2.2.1]heptane-2-carbonitrile ethylene ketal (83)

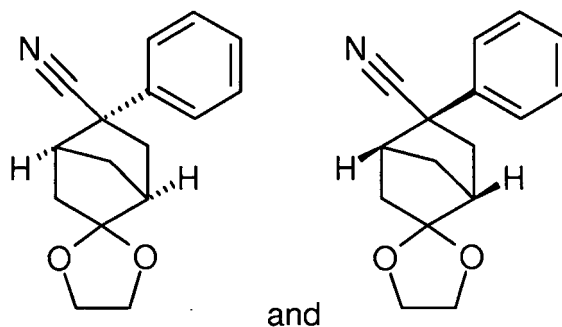
[0239]



[0240] 9.0 g (71 mmol) of 2-cyclopenten-1-one ethylene ketal, 11.4 g (214 mmol) of acrylonitrile and 150 mg (1.4 mmol) of hydroquinone were mixed and heated to 150°C for 1 h under microwave irradiation. The excess of acrylonitrile was removed under reduced pressure and the residue dissolved using 150 mL of diethylether. This solution was washed three times using 50 mL of saturated aqueous Na₂CO₃-solution each, dried over MgSO₄ and evaporated. The resulting oil was dissolved in 200 mL of cyclohexane and 100 mL of diethylether, washed three times using 50 mL of an aqueous 0.1 N NaOH-solution and twice using 100 mL of a saturated aqueous NaCl-solution. The organic layer was dried over MgSO₄, filtered and the solvent evaporated to yield 7.3 g of 83 as a colourless oil.

b) (1S,2S,4S)-5-Oxo-2-phenyl-bicyclo[2.2.1]heptane-2-carbonitrile ethylene ketal and (1R,2R,4R)-5-Oxo-2-phenyl-bicyclo[2.2.1]heptane-2-carbonitrile ethylene ketal (84 and 85)

[0241]



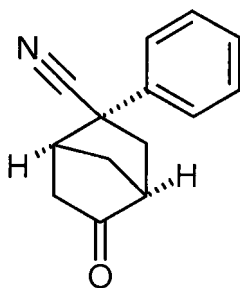
[0242] 7.5 g (42 mmol) of 5-Oxo-bicyclo[2.2.1]heptane-2-carbonitrile ethylene ketal (83) and 4.4 g (46 mmol) of fluorobenzene were dissolved in 10 mL of anhydrous toluene. The mixture was stirred at 65 °C for 20h, then poured into 300 mL of a saturated aqueous NaHCO₃-solution, and extracted twice using 100mL ethyl acetate each. The organic layer was dried using MgSO₄ and evaporated. Chromatography on reversed phase (acetonitrile/water) yielded 3.4g of the racemic mixture as a single diastereomer as colourless oil.

Chromatography on chiral phase (Chiralpak AD-H, 250x4,6 mm) using n-heptane:2-propanol:methanol 5:1:1 yielded 1.4 g of 84 (R_t = 7.4 min) and 1.4 g of 85 (R_t = 9.3 min). R_t = 1.44 min (Method 5). Detected mass: 256.3 (M+H⁺)

The absolute stereochemistry was assigned arbitrarily.

c) (1S,2S,4S)-5-Oxo-2-phenyl-bicyclo[2.2.1]heptane-2-carbonitrile (86)

[0243]

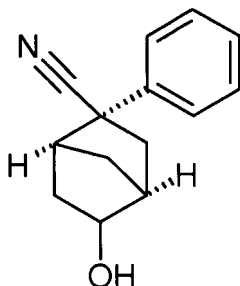


[0244] 1.3 g of (1S,2S,4S)-5-Oxo-2-phenyl-bicyclo[2.2.1]heptane-2-carbonitrile ethylene ketal (84) were dissolved in a mixture of 30 mL THF and 30 mL of a 5% aqueous HCl-solution and kept at ambient temperature for 30h. The mixture was diluted using 100 mL of a saturated aqueous NaCl-solution and 100 mL of ethyl acetate. After separation, the aqueous layer was extracted twice using 50 mL of ethyl acetate each. The organic layer was dried using MgSO_4 and evaporated to give 1.2 g of (86) as a colourless oil.

$[\alpha]_D = +5.6^\circ$ ($c = 0.013$ in methanol), $R_t = 1.27$ min (Method 5).

d) (1S,2S,4S)-5-Hydroxy-2-phenyl-bicyclo[2.2.1]heptane-2-carbonitrile (87)

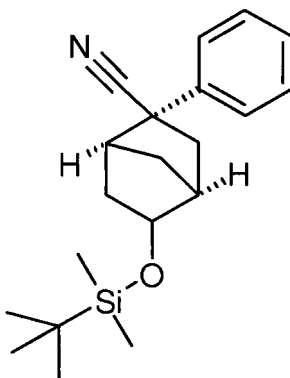
[0245]



[0246] 0.9 g (4.3 mmol) of (1S,2S,4S)-5-Oxo-2-phenyl-bicyclo[2.2.1]heptane-2-carbonitrile (86) were dissolved using 20 mL of ethanol and 161 mg (4.3 mmol) of NaBH_4 was added at -70°C . The mixture was stirred at ambient temperature for 1 h, 100mL of a saturated aqueous NaCl-solution was added and the pH adjusted to 2-3 using aqueous HCl-solution. The mixture was extracted three times using 50 mL of ethyl acetate each. The organic layer was dried over MgSO_4 and evaporated to yield 0.9 g of (87) as a single diastereomer as a colourless oil. $R_t = 0.76$ min (Method 18). Detected mass: 214.1 ($\text{M}+\text{H}^+$)

e) (1S,2S,4S)-5-(tert-Butyl-dimethyl-silanyloxy)-2-phenyl-bicyclo[2.2.1]heptane-2-carbonitrile (88)

[0247]

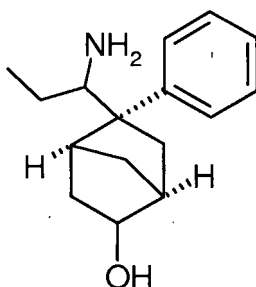


[0248] 0.9 g (4.2 mmol) of (1S,2S,4S)-5-Hydroxy-2-phenyl-bicyclo[2.2.1]heptane-2-carbonitrile (87) and 1.1 g (10.6 mmol) of 2,6-lutidine were dissolved in 40 mL of dichloromethane. 1.3 g (5.1 mmol) of tert-butyldimethylsilyl trifluoromethanesulfonate were added at -10°C. The mixture was stirred at ambient temperature for 17h.

[0249] Afterwards, additional 500 mg of 2,6-lutidine and 600 mg of tert-butyldimethylsilyl trifluoromethanesulfonate were added at -10°C and the mixture stirred at ambient temperature for 48h. Afterwards, additional 1.1 g of 2,6-lutidine and 1.3 g of tert-butyldimethylsilyl trifluoromethanesulfonate were added at -10°C and the mixture stirred at ambient temperature for 24h. The mixture was evaporated, the residue dissolved using 100 mL of ethyl acetate and washed using three times 50 mL of a saturated aqueous Na₂CO₃-solution each, three times 50 mL of a 0.5 N aqueous HCl-solution each and finally once using 50 mL of a saturated aqueous Na₂CO₃-solution. The organic layer was dried using a mixture of MgSO₄ and K₂CO₃, filtered and evaporated. Flash chromatography on silica gel using ethyl acetate/n-heptane 1:2 yielded 970 mg of (88) as a colourless oil. R_f (ethyl acetate/n-heptane 1:2) = 0.8. R_t = 1.32 min (Method 18).

f) (1S,4S,5S)-5-(1-Amino-propyl)-5-phenyl-bicyclo[2.2.1]heptan-2-ol (89)

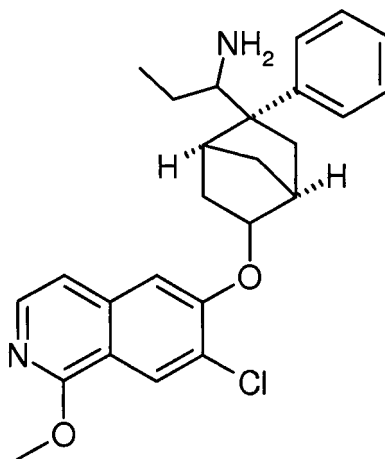
[0250]



[0251] 930mg (2.8 mmol) of (1S,2S,4S)-5-(tert-Butyl-dimethyl-silanyloxy)-2-phenylbicyclo[2.2.1]heptane-2-carbonitrile (88) were dissolved in 10 mL of anhydrous toluene. Afterwards, 5.7 mL of a 1 M solution of ethylmagnesium bromide in THF was added and the mixture was heated under reflux for 12h. The mixture was then treated with 3 mL ethanol and evaporated. The residue was dissolved in 20mL of ethanol and 215 mg (5.7 mmol) of NaBH₄ was added. The mixture was stirred at ambient temperature for 3h and then evaporated. The residue was dissolved using 100 mL of water, the pH adjusted to 3 using aqueous HCl-solution to remove excess NaBH₄ and then adjusted to pH = 12 using saturated aqueous Na₂CO₃-solution. The mixture was extracted three times using 30 mL of t-butylmethylether each. Afterwards, the organic layer was extracted twice using 20 mL of a 1 N aqueous HCl-solution each, the aqueous layer was adjusted to pH>11 using saturated aqueous Na₂CO₃-solution and extracted three times using 30 mL t-butylmethylether each. The organic layer was dried using MgSO₄ and evaporated yielding 200 mg of the desired product 89, used without further purification. R_t = 0.58 min (Method 18).

g) 1-[(1S,2S,4S)-5-(7-Chloro-1-methoxy-isoquinolin-6-yloxy)-2-phenylbicyclo[2.2.1]hept-2-yl]-propylamine (90)

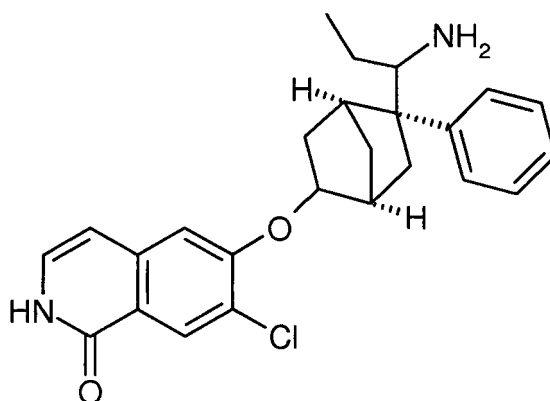
[0252]



[0253] 200 mg (0.82 mmol) of (1S,4S,5S)-5-(1-Amino-propyl)-5-phenyl-bicyclo[2.2.1]heptan-2-ol (89) were dissolved in 5 mL anhydrous dimethylacetamide. Afterwards, 39 mg (1.63 mmol) of NaH were added, followed by the addition of 173 mg (0.82 mmol) of 7-chloro-6-fluoro-1-methoxy-isoquinoline (10). The mixture was stirred at ambient temperature for 20h. Afterwards, 50 mL of a saturated aqueous NaHCO₃-solution were added and the mixture extracted three times using 30 mL ethyl acetate each. The organic layer was dried using MgSO₄ and evaporated. The residue was purified using chromatography on reversed phase (acetonitrile/water). The product-containing fractions were evaporated to half of the original volume, 10 mL of a saturated aqueous Na₂CO₃-solution was added and the mixture extracted three times using 20 mL of ethyl acetate each. The organic layer was dried using MgSO₄, filtered and evaporated yielding 34 mg of the desired product 90. R_t = 0.86 min (Method 18). Detected mass: 437.3 (M+H⁺)

h) 6-[(1S,4S,5S)-5-(1-Amino-propyl)-5-phenyl-bicyclo[2.2.1]hept-2-yloxy]-7-chloro-2H-isoquinolin-1-one (Example 100)

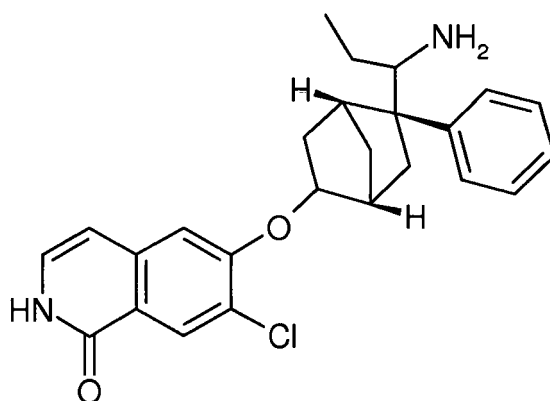
[0254]



[0255] 35 mg of 1-[(1S,2S,4S)-5-(7-Chloro-1-methoxy-isoquinolin-6-yloxy)-2-phenylbicyclo[2.2.1]hept-2-yl]-propan-1-amine (90) were dissolved using 1 mL of 2-propanol and 1 mL of a 1 N aqueous HCl-solution. The mixture was heated to 100 °C for 1 h under microwave irradiation. Afterwards, 20 mL of water were added and the mixture freeze dried. The residue was once again treated with 20 mL of water and freeze dried to yield 34 mg of the desired product as its hydrochloride. R_t = 0.75 min (Method 18). Detected mass: 423.2 (M+H⁺)

Example 101: 6-[(1R,4R,5R)-5-(1-Amino-propyl)-5-phenyl-bicyclo[2.2.1]hept-2-yloxy]-7-chloro-2H-isoquinolin-1-one

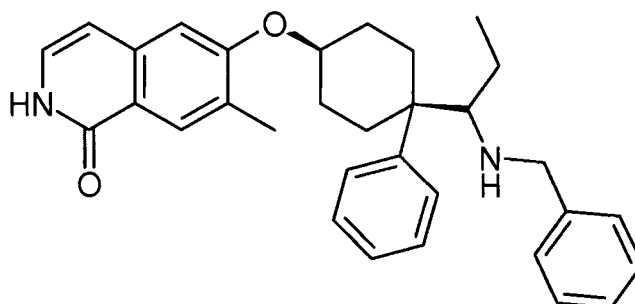
[0256]



[0257] Example 101 has been synthesized as its hydrochloride in analogy to the synthesis of example 100 starting from 7-chloro-6-fluoro-1-methoxy-isoquinoline (10) and (1R,2R,4R)-5-oxo-2-phenyl-bicyclo[2.2.1]heptane-2-carbonitrile ethylene ketal (85). R_t = 0.75 min (Method 18). Detected mass: 423.2 (M+H⁺)

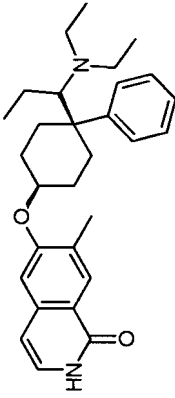
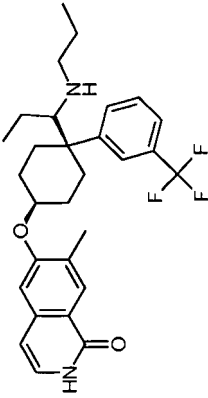
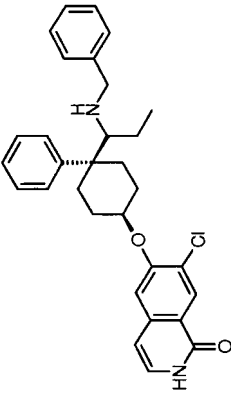
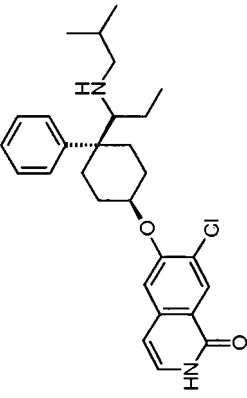
Example 102: cis-6-[4-(1-Benzylamino-propyl)-4-phenyl-cyclohexyloxy]-7-methyl-2H-isoquinolin-1-one

[0258]

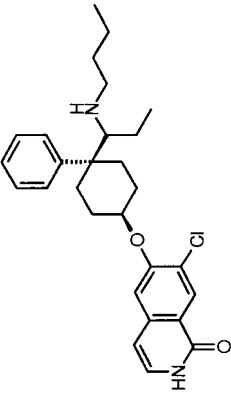
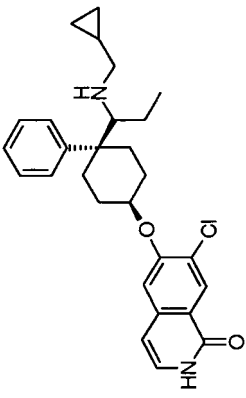


[0259] 60 mg of Example 11 were dissolved in 850 μ L of methanol, then 39 μ L of triethylamine, 80 μ L of acetic acid, 50 mg of powdered molecular sieves and 43 μ L of benzaldehyde were added and the mixture was allowed to stir for 1 h. A solution of 26 mg of sodium cyanoborohydride in 200 μ L of methanol was added and the mixture was stirred at 40°C for 5 min. The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in 50 mL of dichloromethane and washed with saturated sodium bicarbonate solution. The aqueous phase was reextracted twice with dichloromethane. The combined organic layer was dried over magnesium sulphate, filtered, evaporated and the crude material was purified by reversed phase HPLC (acetonitrile/water) to yield 27 mg of the desired product as trifluoroacetic acid salt. $R_t = 2.94$ min (Method 2). Detected mass: 481.4 ($M+H^+$).

[0260] The following examples were obtained in a similar fashion as described for example 102, using the respective isoquinolines and aldehydes as starting materials:

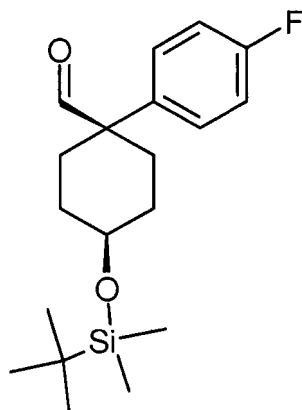
Ex. No.	Product	Start. Mat.	Aldehyde	Chemical Name	[M+H ⁺]	R _t [min]	Method
103		Ex. 11	Acetaldehyde	cis-6-[4-(1-Diethylaminopropyl)-4-phenyl-cyclohexyloxy]-7-methyl-2H-isoquinolin-1-one	447.4	2.73	2
104		Ex. 86	Propanal	cis-7-Methyl-6-[4-(1-propyl amino-propyl)-4-(3-trifluoromethylphenyl)-cyclo hexyloxy]-2H-isoquinolin-1-one	501.2	1.50	10
105		Ex. 3	Benzaldehyde	cis-6-[4-(1-Benzylaminopropyl)-4-phenyl(cyclohexyloxy)-7-chloro-2H-isoquinolin-1-one	501.3	1.47	10
106		Ex. 3	Isobutyraldehyde	cis-7-Chloro-6-[4-(1-isobutyl amino-propyl)-4-phenyl(cyclohexyloxy)-2H-iso quinolin-1-one	467.3	1.45	10

(continued)

Ex. No.	Product	Start. Mat.	Aldehyde	Chemical Name	[M+H ⁺]	R _f /[min]	Method
107		Ex. 3	Butanal	cis-6-[4-(1-Butylaminopropyl)-4-phenyl-cyclo hexyloxy]-7-chloro-2H-isoquinolin-1-one	501.3	1.46	10
108		Ex. 3	Cyclo propyl carbox aldehy de	cis-7-Chloro-6-{4-[1-(cyclo propylmethylamino)-propyl]-4-phenylcyclohexyloxy}-2H-isoquinolin-1-one	465.3	1.43	10

cis-4-(tert-Butyl-dimethyl-silanyloxy)-1-(4-fluoro-phenyl)-cyclohexanecarb- aldehyde (91)

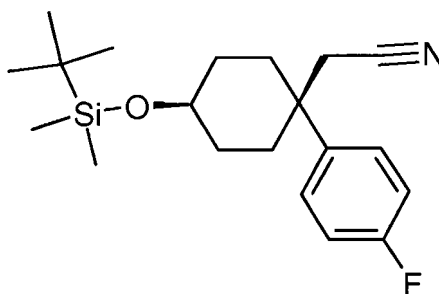
[0261]



[0262] To a solution of 9.74 g (29.2 mmol) of cis-4-(tert-butyl-dimethyl-silanyloxy)-1-(4-fluorophenyl)-cyclohexane-carbonitrile (78) in 290 mL of dichloromethane at -70 °C were added over a period of 20 min 73 mL (73 mmol) of a solution of diisobutylaluminium hydride in dichloromethane (1 M). The reaction mixture was stirred for 1 h at -70 °C, before 250 mL of 10% aqueous potassium sodium tartrate solution were added and the resulting biphasic system was vigorously stirred for 2 h at room temperature. 200 mL of ethyl acetate were added and the phases were separated. The aqueous phase was extracted with 150 mL of ethyl acetate and the combined organic phases were dried over magnesium sulphate, filtered and concentrated. The resulting oil was purified by silica gel chromatography (heptanes:ethyl acetate) to give 8.38 g of the desired product. $R_f = 1.09$ min (Method 17). Detected mass: 337.2 ($M+H^+$).

cis-[4-(tert-Butyl-dimethyl-silanyloxy)-1-(4-fluoro-phenyl)-cyclohexyl]-acetonitrile (92)

[0263]

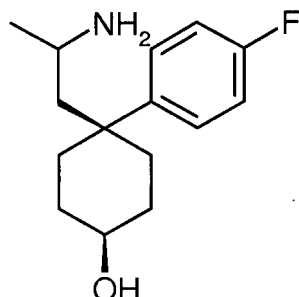


[0264] To an ice-cold solution of 6.60 g (19.6 mmol) of cis-4-(tert-butyl-dimethyl-silanyloxy)-1-(4-fluoro-phenyl)-cyclohexanecarbaldehyde (91) in 50 mL of dry methanol were added portionwise 1.48 g (39.2 mmol) of sodium borohydride. The reaction mixture was stirred for 1 h at 0 °C, then 16h at room temperature, before being quenched by addition of 70 mL of water. The solution was extracted three times with ethyl acetate (100 mL each). The organic phases were combined, washed with brine, dried over magnesium sulphate, filtered and evaporated to dryness. The resulting alcohol (6.17 g crude) was dissolved in 50 mL of dry dichloromethane and cooled to 0°C. 2.56 mL (1.84 g, 18.2 mmol) of triethylamine were added and the mixture stirred for 5 min. Then, 3.53 mL (5.22 g, 45.6 mmol) of methanesulfonylchloride was added dropwise and the solution was stirred for 2.5 h at 0 °C. The reaction mixture was treated with 50 mL of water and stirred for 30 min at room temperature. The phases were separated and the aqueous phase was extracted twice with 100 mL dichloromethane. The organic phases were combined, washed with brine, dried over magnesium sulphate, filtered and evaporated to dryness. The crude product was purified by silica gel chromatography (heptanes:ethyl acetate) to give 5.20 g of the desired mesylate, which was dissolved in 200 mL of dry dimethylformamide and treated with 4.06 g (62.4 mmol) of potassium cyanide and 6.60 g (25.0 mmol) of 18-crown-6. The orange solution was heated to 155 °C for 36h and stirred 16h at room temperature before being poured onto 200 mL of a mixture of water and ice. The mixture was extracted twice with ethyl acetate. The organic phases were combined, dried over

magnesium sulphate, filtered and concentrated. The crude product was purified by silica gel chromatography (heptanes:ethyl acetate) to give 1.22 g of the desired product 92. $R_t = 1.04$ min (Method 17). Detected mass: 348.2 ($M+H^+$).

cis-4-(2-Amino-propyl)-4-(4-fluoro-phenyl)-cyclohexanol (93)

[0265]

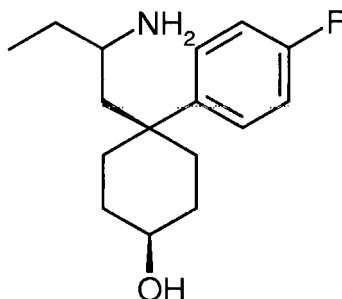


[0266] Under argon, 260 mg (0.75 mmol) of cis-[4-(tert-butyl-dimethyl-silanyloxy)-1-(4-fluorophenyl)-cyclohexyl]-acetonitrile (92) were dissolved in 5 mL of absolute toluene. Then, 500 μ L of methylmagnesium bromide (3M in diethylether) were added dropwise and the reaction mixture was heated to 80 °C for 2h. After cooling to room temperature, 3 mL of dry methanol were added. After a period of 10 min, 28.3 mg (1.45 mmol) of sodium borohydride were added and the mixture was stirred for 3h at room temperature. The reaction was quenched by addition of 1 M aqueous sodium hydroxide solution and extracted three times with diethylether (100 mL each).

The combined organic phases were concentrated to a volume of approximately 80 mL and 50 mL of 2N aqueous hydrochloric acid were added. The biphasic system was stirred vigorously at room temperature for 3h. The phases were separated, the aqueous layer was adjusted to pH 12 by addition of 5N sodium hydroxide solution and extracted three times with a 3:1 mixture of dichloromethane and 2-propanol (80 mL each). The combined organic layers were evaporated to give 92 mg of the desired product, which was used directly in the next step. $R_t = 0.64$ min (Method 18). Detected mass: 252.2 ($M+H^+$).

cis-4-(2-Amino-butyl)-4-(4-fluoro-phenyl)-cyclohexanol (94)

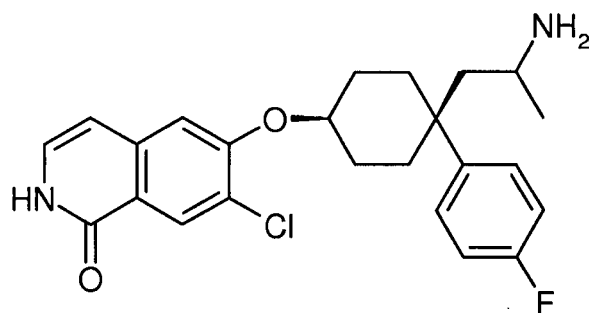
[0267]



[0268] 355 mg of cis-4-(2-Amino-butyl)-4-(4-fluoro-phenyl)-cyclohexanol (94) were prepared analogously to the preparation of cis-4-(2-amino-propyl)-4-(4-fluoro-phenyl)-cyclohexanol (93), starting from 500 mg (1.44 mmol) of cis-[4-(tert-butyl-dimethylsilanyloxy)-1-(4-fluoro-phenyl)-cyclohexyl]-acetonitrile (92), 960 μ L (2.88 mmol) of ethylmagnesium bromide (3M in diethylether) and 54.4 mg (2.88 mmol) of sodium borohydride. $R_t = 0.66$ min (Method 18). Detected mass: 266.2 ($M+H^+$).

Example 109: cis-6-[4-(2-Amino-propyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one

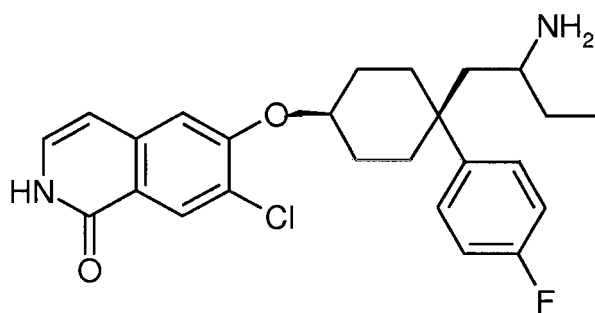
[0269]



[0270] Example 109 was synthesized using the reaction sequence as described for the synthesis of Example 1. 90 mg of cis-4-(2-amino-propyl)-4-(4-fluoro-phenyl)-cyclohexanol (93) and 79.6 mg of 7-chloro-6-fluoro-1-methoxy-isoquinoline (10) were used to give 35 mg of Example 109 as hydrochloride. $R_t = 1.31$ min (Method 16). Detected mass: 429.2 ($M+H^+$).

Example 110: cis-6-[4-(2-Amino-butyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one

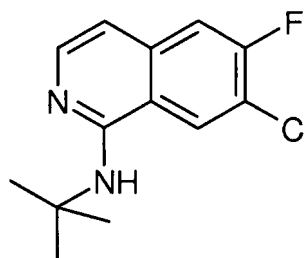
[0271]



[0272] Example 110 was obtained as hydrochloride following the reaction sequence as used for the synthesis of Example 109, starting from cis-4-(2-amino-butyl)-4-(4-fluorophenyl)-cyclohexanol (94) and 7-chloro-6-fluoro-1-methoxy-isoquinoline (10). $R_t = 1.45$ min (Method 16). Detected mass: 443.2 ($M+H^+$).

tert-Butyl-(7-chloro-6-fluoro-isoquinolin-1-yl)-amine (95)

[0273]

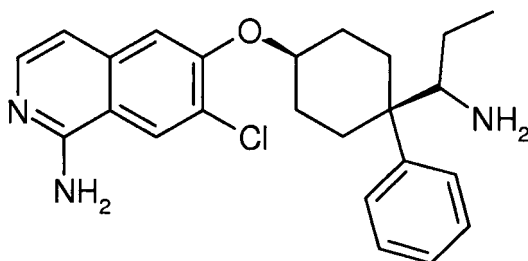


[0274] A solution of 5.0 g (25.3 mmol) of 7-chloro-6-fluoro-isoquinoline-2-oxide (9) in 120 mL of benzotrifluoride was treated with 15.9 mL (11.1 g, 152 mmol) of tert-butylamine and cooled to 0 °C. Then, 17.3 g (53.1 mmol) of p-toluenesulfonic anhydride were added portionwise with temperature control (<10 °C). The reaction mixture was stirred at room temperature for 16h, before being cooled to 0 °C and another 8.0 mL (76.1 mmol) of tert-butylamine and 8.26 g (25.3 mmol) of p-toluenesulfonic anhydride were added. The reaction mixture was stirred for 24h at room temperature, then concentrated and partitioned between 120 mL of water and 150 mL of dichloromethane. The phases were separated and the organic phase was washed eight times with 3N aqueous sodium hydroxide, to extract excess p-toluenesulfonic acid, dried over magnesium sulphate, filtered and evaporated to dryness. The crude product was purified twice by silica gel chromatography (dichloromethane:methanol) to give 277 mg of pure desired product (95) and 714 mg of the product

slightly contaminated with p-toluenesulfonic acid. $R_t = 2.35$ min (Method 2). Detected mass: 253.1 ($M+H^+$).

Example 111: cis-6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-chloro-isoquinolin-1-ylamine

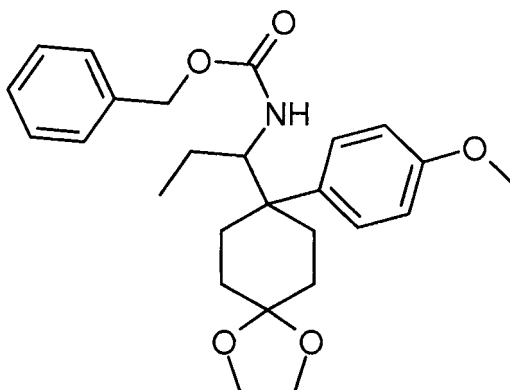
[0275]



[0276] 58 mg of Example 111 were obtained following a reaction sequence with NaH-mediated coupling and acidic deprotection in the microwave similar to the one used for the synthesis of Example 1, starting from 102 mg (0.44 mmol) of cis-4-(1-aminopropyl)-4-phenylcyclohexanol (6) and 100 mg (0.40 mmol) of tert-butyl-(7-chloro-6-fluoroisoquinolin-1-yl)-amine (95). $R_t = 0.84$ min (Method 11). Detected mass: 410.3 ($M+H^+$).

{1-[8-(4-Methoxy-phenyl)-1,4-dioxa-spiro[4.5]dec-8-yl]-propyl}-carbamic acid benzyl ester (96)

[0277]

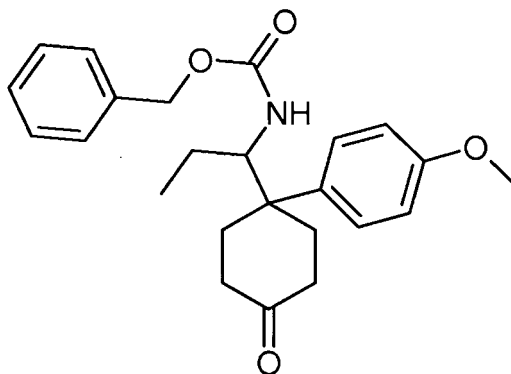


[0278] 5.0 g (18.3 mmol) of 8-(4-methoxy-phenyl)-1,4-dioxa-spiro[4.5]decane-8-carbonitrile (synthesized from 1-(4-methoxy-phenyl)-4-oxo-cyclohexanecarbonitrile in a similar fashion as described for 15) were dissolved in 20 mL of absolute toluene. Then, 12.2 mL (36.6 mmol) of ethylmagnesium chloride (3M in THF) were added dropwise and the reaction mixture was heated to 90 °C for 5h. After cooling to -15 °C, 10 mL of dry methanol were added. After a period of 10 min, 1.37 g (36.3 mmol) of sodium borohydride were added portionwise at 0 °C and the mixture was stirred for 16h at room temperature. The reaction was quenched by addition of 1 M aqueous sodium hydroxide solution (100 mL) and extracted three times with diethylether (150 mL each). The combined organic phases were dried over magnesium sulphate, filtered and the solvent evaporated.

The crude amine (4.90 g) was dissolved in 55 mL of dry dichloromethane, cooled to -78 °C and 2.46 mL (1.79 g, 17.6 mmol) of triethylamine and 2.71 mL (2.74 g, 16.0 mmol) of benzylchloroformate were added. The reaction mixture was warmed to room temperature and stirred for 2h. Then, 100 mL of water were added and the mixture was extracted three times with ethyl acetate. The combined organic phases were dried over magnesium sulphate, filtered and concentrated to give the crude product (96), which was used directly in the next step. $R_t = 1.09$ min (Method 18). Detected mass: 440.4 ($M+H^+$).

{1-[1-(4-Methoxy-phenyl)-4-oxo-cyclohexyl]-propyl}-carbamic acid benzyl ester (97)

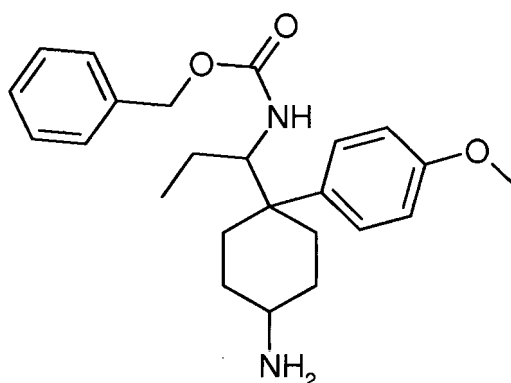
[0279]



[0280] 534 mg of {1-[8-(4-Methoxy-phenyl)-1,4-dioxo-spiro[4.5]dec-8-yl]-propyl}-carbamic acid benzyl ester (96) were dissolved in 1 mL of a 2:1 mixture of acetone and 6N aqueous hydrochloric acid. The reaction mixture was stirred for 16h at room temperature, then dropped into 150 mL of saturated aqueous sodium bicarbonate solution. The phases were separated and the aqueous phase was extracted three times with dichloromethane (100 mL each). The combined organic phases were dried over magnesium sulphate, filtered and concentrated to give the ketone 97. $R_t = 1.58$ min (Method 19). Detected mass: 396.3 ($M+H^+$).

{1-[4-Amino-1-(4-methoxy-phenyl)-cyclohexyl]-propyl}-carbamic acid benzyl ester (98)

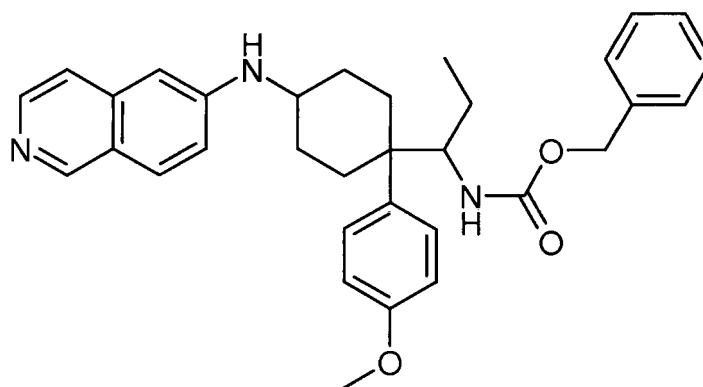
[0281]



[0282] 200 mg (0.51 mmol) of the ketone (97) were dissolved in 1.5 mL of absolute methanol, then 390 mg (5.06 mmol) of ammonium acetate and 31.8 mg (0.51 mmol) of sodium cyanoborohydride were added, and the mixture was stirred at room temperature for 2h. The reaction mixture was evaporated, the residue dissolved in 50 mL of 1 N aqueous sodium hydroxide and extracted twice with 100 mL of dichloromethane. The combined organic layer was dried over magnesium sulphate, filtered, and evaporated to give 150 mg of the title compound 98 in a purity sufficient to be used directly in the next step. $R_t = 1.18$ min (Method 19). Detected mass: 397.3 ($M+H^+$).

{1-[4-(Isoquinolin-6-ylamino)-1-(4-methoxy-phenyl)-cyclohexyl]-propyl}-carbamic acid benzyl ester (99)

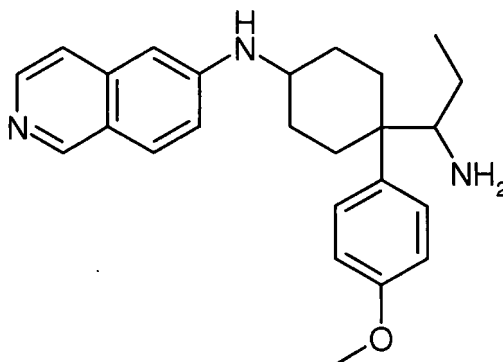
[0283]



[0284] In 1 mL of absolute toluene were dissolved 66.0 mg (0.32 mmol) of 6-bromoisoquinoline, 151 mg (380 μmol) of {1-[4-amino-1-(4-methoxy-phenyl)-cyclohexyl]-propyl}-carbamic acid benzyl ester (98), and 155 mg (476 μmol) of cesium carbonate. The solution was degassed twice, then 2.14 mg (9.5 μmol) of palladium acetate and 8.89 mg (14.3 μmol) of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl were added and the reaction mixture was heated to 100 °C until complete conversion could be observed. The mixture was evaporated, then redissolved in 50 mL of dichloromethane and washed twice with 50 mL of saturated aqueous sodium bicarbonate solution. The organic phase was dried over magnesium sulphate, filtered, concentrated and purified by silica gel chromatography (dichloromethane:methanol) to give 48 mg of the pure desired product. R_t = 1.38 min (Method 19). Detected mass: 524.4 ($M+H^+$).

Example 112: [4-(1-Amino-propyl)-4-(4-methoxy-phenyl)-cyclohexyl]-isoquinolin-6-yl-amine

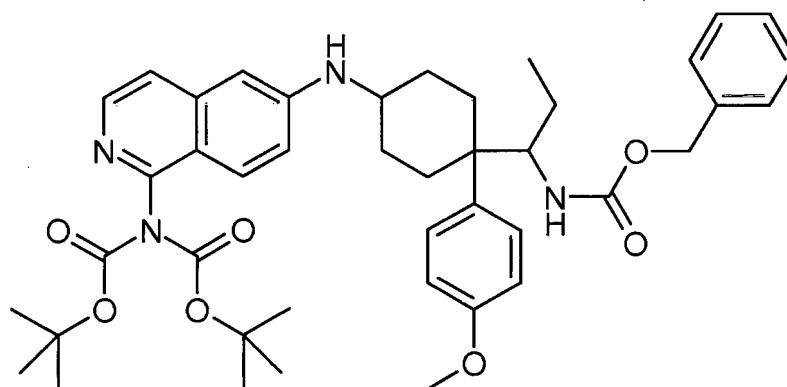
[0285]



[0286] 48 mg (91.7 μmol) of {1-[4-(Isoquinolin-6-ylamino)-1-(4-methoxy-phenyl)-cyclohexyl]-propyl}-carbamic acid benzyl ester (99) were dissolved in 300 μL of dry methanol and 9.7 μg of palladium on activated charcoal (10%) were added. The mixture was stirred under a hydrogen atmosphere until conversion was complete. The catalyst was filtered off and the reaction mixture was evaporated to dryness to give the title compound. R_t = 0.89 min (Method 19). Detected mass: 390.3 ($M+H^+$).

1-(Di-tert-butyloxycarbonyl)-amino-[4-(1-amino-propyl)-4-(4-methoxy-phenyl)-cyclohexyl]-isoquinolin-6-yl-amine (100)

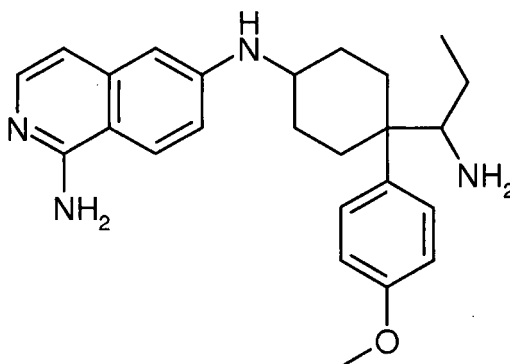
[0287]



[0288] 30 mg (83.5 μmol) of 1-(di-tert-butyloxycarbonyl)-amino-isoquinolin-6-amine were dissolved in 135 μL of abs. methanol, then 23 μL (16.9 mg, 167 μmol) of triethylamine, 47.7 μL (50.1 mg, 835 μmol) of acetic acid, 20 mg of powdered molecular sieves and 99 mg (250 μmol) of (97) were added and the mixture was allowed to stir for 1 h. A solution of 15.7 mg (250 μmol) of sodium cyanoborohydride in 50 μL of methanol was added and the mixture was stirred at 70°C for 10 h. Then, another 50 mg (125 μmol) of (97) followed by a portion of 15.7 mg (250 μmol) of sodium cyanoborohydride in 50 μL of methanol were added and the mixture was allowed to stir for 1 h at 70 °C. The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in 50 mL of dichloromethane and washed with saturated sodium bicarbonate solution. The aqueous phase was reextracted three times with dichloromethane. The combined organic layer was dried over magnesium sulphate, filtered, evaporated and the crude material was purified by reversed phase HPLC (acetonitrile/water) to yield 5 mg of the desired product as trifluoroacetic acid salt. $R_t = 1.65$ min (Method 19). Detected mass: 739.3 ($M+H^+$).

Example 113: 1-Amino-[4-(1-amino-propyl)-4-(4-methoxy-phenyl)-cyclohexyl]-isoquinolin-6-yl-amine

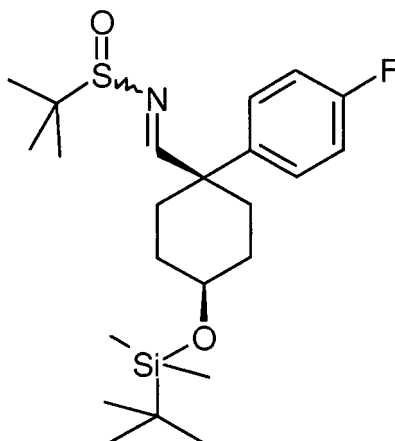
[0289]



[0290] 5 mg (6.77 μmol) of 1-(Di-tert-butyloxycarbonyl)-amino-[4-(1-amino-propyl)-4-(4-methoxy-phenyl)-cyclohexyl]-isoquinolin-6-yl-amine (100) were dissolved in 500 μL of dry methanol and 5.0 mg of palladium on activated charcoal (10%) were added. The mixture was stirred under a hydrogen atmosphere until conversion was complete. The catalyst was filtered off and the reaction mixture was evaporated to dryness. The solid residue was treated with 500 μL of 4N hydrochloric acid in dioxane and stirred at room temperature until complete deprotection could be observed. The reaction mixture was evaporated, water was added and the mixture was lyophilized. The residue was taken up in water and lyophilized again to give 1.2 mg of the desired product as hydrochloride. $R_t = 0.98$ min (Method 19). Detected mass: 405.3 ($M+H^+$).

cis-2-Methyl-propane-2-sulfinic acid 1-[4-(tert-butyl-dimethyl-silanyloxy)-1-(4-fluorophenyl)-cyclohexyl]-methylideneamide (101)

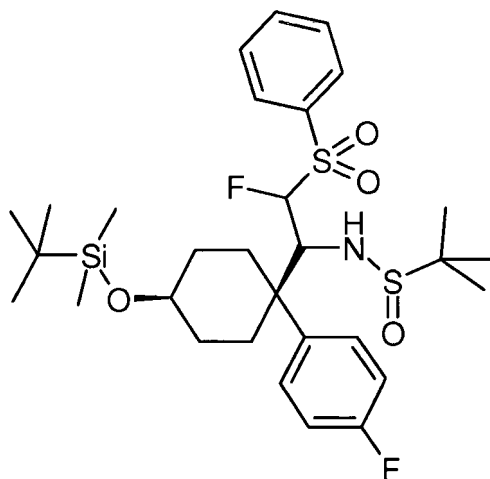
[0291]



[0292] To a solution of 3.0 g (8.92 mmol) of cis-4-(tert-butyl-dimethyl-silanyloxy)-1-(4-fluorophenyl)-cyclohexanecarbaldehyde (91) in 26 mL of tetrahydrofuran were added 1.19 g (9.81 mmol) of 2-methyl-2-propanesulfinamide and 4.31 mL (4.69 g, 13.4 mmol) of titanium(IV) ethoxide. The resulting mixture was stirred for 16h under reflux, before being treated with 30 mL of water. The resulting suspension was filtered through celite. The filter cake was rinsed with 200 mL of ethyl acetate and 60 mL of water. The phases were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulphate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO₂, 0% → 100% ethyl acetate in heptane) to yield 1.64 g of the title compound (101). $R_t = 1.18$ min (Method 17). Detected mass: 440.2 (M+H⁺).

cis-2-Methyl-propane-2-sulfinic acid {2-benzenesulfonyl-1-[4-(tert-butyl-dimethylsilanyloxy)-1-(4-fluoro-phenyl)-cyclohexyl]-2-fluoro-ethyl}-amide (102)

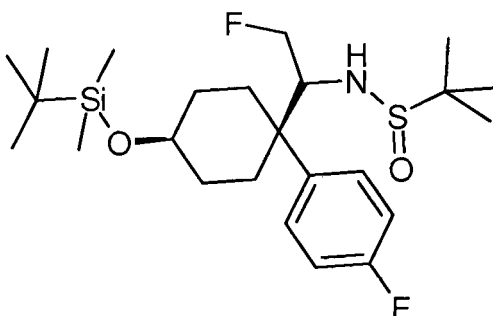
[0293]



[0294] A solution of 1.75 g (3.98 mmol) of cis-2-methyl-propane-2-sulfinic acid 1-[4-(tert-butyl-dimethyl-silanyloxy)-1-(4-fluoro-phenyl)-cyclohexyl]-methylideneamide (101) and 693 mg (3.98 mmol) of fluoromethyl-phenyl-sulfone in 40 mL of dry tetrahydrofuran was cooled to -78 °C and 4.17 mL (4.17 mmol) of a 1 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran were added. The mixture was stirred for 1 h at -78 °C before being quenched by addition of saturated aqueous ammonium chloride solution and extracted twice with ethyl acetate. The combined organic layers were dried over magnesium sulphate, filtered, and concentrated *in vacuo* to give 2.45 g of the crude title compound (102) as diastereomeric mixture. $R_t = 3.31$ min (Method 12). Detected mass: 614.3 (M+H⁺)

cis-2-Methyl-propane-2-sulfinic acid {1-[4-(tert-butyl-dimethyl-silanyloxy)-1-(4-fluorophenyl)-cyclohexyl]-2-fluoro-ethyl}-amide (103)

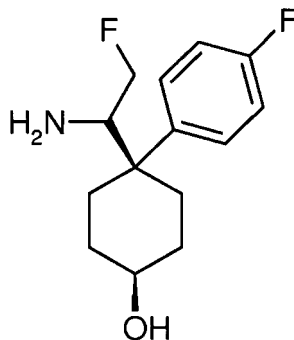
[0295]



[0296] 1.70 g (2.77 mmol) of cis-2-Methyl-propane-2-sulfinic acid {2-benzenesulfonyl-1-[4-(tert-butyl-dimethyl-silanyloxy)-1-(4-fluoro-phenyl)-cyclohexyl]-2-fluoro-ethyl}-amide (102) was dissolved in 30 mL of dry methanol and 1.57 g (11.1 mmol) of dibasic sodium phosphate were added. The suspension was cooled to -20 °C, and treated with 2.48 g of sodium mercury amalgam (5% mercury). The reaction mixture was stirred at 0 °C for 16h and another 620 mg of sodium amalgam were added. After stirring for 24h at room temperature, the solution was decanted from the solids, evaporated to dryness and the residue partitioned between 50 mL of brine and 100 mL of diethylether. The organic layer was dried over sodium sulphate, filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 0% → 100% ethyl acetate in heptane) yielded 300 mg of the title compound (103). R_t = 1.07 min (Method 17). Detected mass: 474.4 (M+H⁺).

cis-4-(1-Amino-2-fluoro-ethyl)-4-(4-fluoro-phenyl)-cyclohexanol (104)

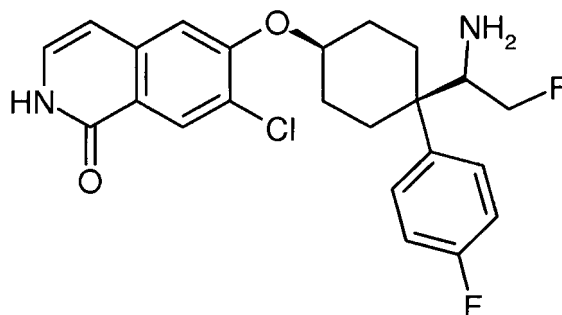
[0297]



[0298] A solution of 300 mg (0.63 mmol) of cis-2-methyl-propane-2-sulfinic acid {1-[4-(tert-butyl-dimethyl-silanyloxy)-1-(4-fluoro-phenyl)-cyclohexyl]-2-fluoro-ethyl}-amide (103) in 3 mL of 2-propanol was treated with 3 mL of 6N aqueous hydrochloric acid and stirred for 18h at room temperature. The mixture was washed with 50 mL of diethylether and lyophilized, then taken up in water and lyophilized again to give the title compound (104) as its hydrochloride. R_t = 0.49 min (Method 18). Detected mass: 256.3 (M+H⁺).

Example 114: cis-6-[4-(1-Amino-2-fluoro-ethyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one

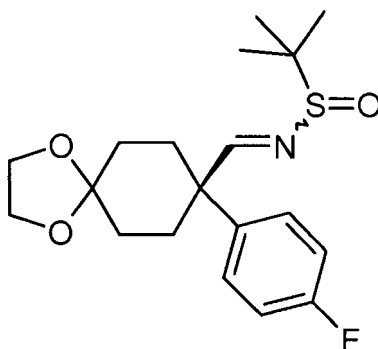
[0299]



[0300] Example 114 was synthesized using the reaction sequence as described for the synthesis of Example 1. 209 mg of cis-4-(1-amino-2-fluoro-ethyl)-4-(4-fluoro-phenyl)-cyclohexanol (104) and 158 mg of 7-chloro-6-fluoro-1-methoxyisoquinoline (10) were used to give 132 mg of Example 114 as its hydrochloride. $R_t = 1.79$ min (Method 12). Detected mass: 433.2 ($M+H^+$)

2-Methyl-propane-2-sulfinic acid 8-(4-fluoro-phenyl)-1,4-dioxaspiro[4.5]dec-8-ylmethyleamide (105)

[0301]

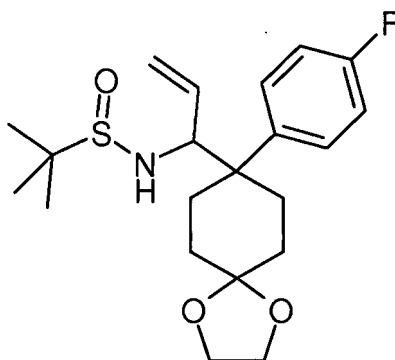


[0302] To a solution of 10.0 g (38.3 mmol) of 8-(4-fluoro-phenyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (15) in 44 mL of tetrahydrofuran at -78°C were slowly added 76.5 mL (76.5 mmol) of a 1 M solution of diisobutylaluminum hydride in toluene and the reaction was allowed to warm to 0°C over a period of 3h. The mixture was recooled to -78°C , neutralized by dropwise addition of a 10% aqueous citric acid solution and warmed to room temperature over 15h. The mixture was extracted three times with methyl-tert.butyl ether (50 mL each), the combined organics were dried over magnesium sulphate, filtered and evaporated to give 8-(4-fluoro-phenyl)-1,4-dioxaspiro[4.5]decane-8-carbaldehyde.

The crude aldehyde was dissolved in 113 mL of tetrahydrofuran and 5.09 g (42.0 mmol) of 2-methyl-2-propanesulfinamide and 12.0 mL (13.1 g, 57.3 mmol) of titanium(IV) ethoxide were added. The resulting mixture was stirred for 3h under reflux and 16h at room temperature, before being treated with 30 mL of water and filtered through celite. The filter cake was washed with 200 mL of ethyl acetate and 60 mL of water, the phases were separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over magnesium sulphate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2 , 0% \rightarrow 100% ethyl acetate in heptane) to yield 3.20 g of the title compound (105). $R_t = 1.01$ min (Method 18). Detected mass: 368.3 ($M+H^+$).

2-Methyl-propane-2-sulfinic acid {1-[8-(4-fluoro-phenyl)-1,4-dioxaspiro[4.5]dec-8-yl]-allyl}-amide (106)

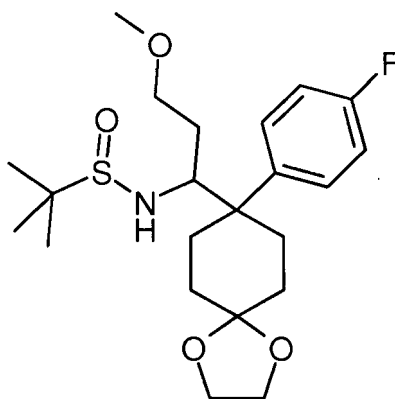
[0303]



[0304] Under argon, 2.00 g (5.44 mmol) of 2-methyl-propane-2-sulfinic acid 8-(4-fluorophenyl)-1,4-dioxa-spiro[4.5]dec-8-ylmethyleneamide (105) were dissolved in 27 mL of absolute tetrahydrofuran. Then, 5.99 mL (5.99 mmol) of vinylmagnesium bromide (1 M in tetrahydrofuran) were added dropwise at 0 °C and the reaction mixture was stirred for 17h at room temperature. Another 3 mL (3.00 mmol) of vinylmagnesium bromide (1 M in tetrahydrofuran) were added and the mixture stirred for 20h at room temperature. The reaction mixture was cooled to 0 °C and 15 mL of saturated aqueous sodium sulphate solution were added. The suspension was filtered over celite, the organic layer was dried over magnesium sulphate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO₂, 0% → 100% ethyl acetate in heptane) to yield 1.09 g of (106). R_f = 0.96 min (Method 18). Detected mass: 396.4 (M+H⁺).

2-Methyl-propane-2-sulfinic acid {1-[8-(4-fluoro-phenyl)-1,4-dioxa-spiro[4.5]dec-8-yl]-3-methoxy-propyl}-amide (107)

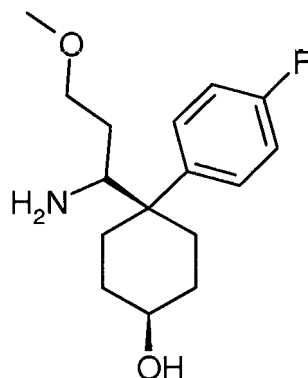
[0305]



[0306] 16.5 mL (8.23 mmol) of a 0.5M solution of 9-BBN in tetrahydrofuran were added to a solution of 1.09 g (2.74 mmol) of 2-methyl-propane-2-sulfinic acid {1-[8-(4-fluorophenyl)-1,4-dioxa-spiro[4.5]dec-8-yl]-allyl}-amide (106) in 5 mL THF at 0 °C. The reaction mixture was allowed to warm to room temperature over night, before being cooled to 0 °C. Then, 20 mL of 3M aqueous sodium hydroxide and 7.5 mL of 30% aqueous hydrogen peroxide were added slowly, and the mixture was stirred for 16 h at room temperature. The mixture was extracted twice with 50 mL of ethyl acetate, washed with water and saturated sodium chloride solution, dried over magnesium sulfate and concentrated *in vacuo*. The crude alcohol was dissolved in 5 mL of tetrahydrofuran and added slowly to a suspension of 131 mg (4.46 mmol) of sodium hydride (60%) in 5 mL tetrahydrofuran at 0 °C. 515 μ L (8.20 mmol) of iodomethane were added, and after stirring for 16 h at room temperature another 50 mg of sodium hydride (60%) were added. The reaction mixture was stirred for 1 h at room temperature, then 30 mL of methanol and 15 mL of aqueous ammonium hydroxide solution (33%) were added. The reaction mixture was evaporated to dryness and lyophilized from water to give 1.17 g of the title compound (107) in a purity sufficient for further conversion. R_f = 0.93 min (Method 18). Detected mass: 428.2 (M+H⁺).

cis-4-(1-Amino-3-methoxy-propyl)-4-(4-fluoro-phenyl)-cyclohexanol (108)

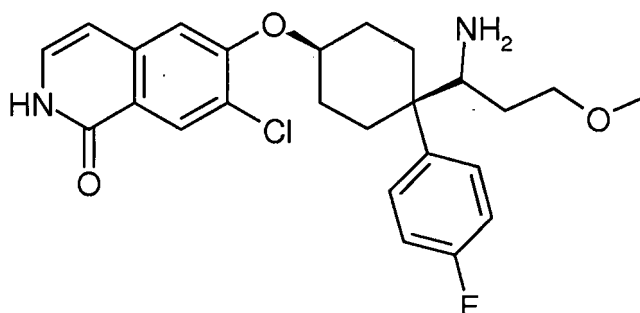
[0307]



[0308] A solution of 1.16 g (2.71 mmol) of 2-methyl-propane-2-sulfinic acid {1-[8-(4-fluorophenyl)-1,4-dioxaspiro[4.5]dec-8-yl]-3-methoxy-propyl}-amide (107) in a mixture of 5 mL of acetic acid and 1.25 mL of water was heated in the microwave oven at 100 °C for 5 min. The mixture was cooled to room temperature and slowly poured onto 100 mL of cold saturated aqueous sodium bicarbonate solution. The mixture was extracted three times with a 3:1 mixture of dichloromethane and ethanol (50 mL each). The organic phase was concentrated *in vacuo* to remove the dichloromethane and 203 mg (5.37 mmol) of sodium borohydride were added. The reaction mixture was stirred at room temperature overnight, when another 203 mg (5.37 mmol) of sodium borohydride were added. After 18h at room temperature, the reaction mixture was quenched with water, concentrated *in vacuo* and lyophilized twice from water to give the title compound (108), which was used crude in the next step. $R_t = 1.95$ min (Method 2). Detected mass: 282.2 ($M+H^+$).

Example 115: cis-6-[4-(1-Amino-3-methoxy-propyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one

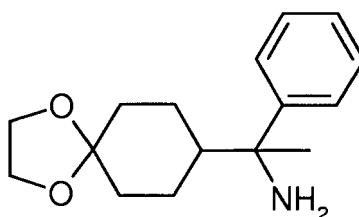
[0309]



[0310] Example 115 was synthesized using the reaction sequence as described for the synthesis of Example 1. 414 mg of cis-4-(1-amino-3-methoxy-propyl)-4-(4-fluorophenyl)-cyclohexanol (108) and 283 mg of 7-chloro-6-fluoro-1-methoxy-isoquinoline (10) were used to give 66.6 mg of Example 115 as its hydrochloride. $R_t = 1.88$ min (Method 12). Detected mass: 459.3 ($M+H^+$)

1-(1,4-Dioxaspiro[4.5]dec-8-yl)-1-phenyl-ethylamine (26)

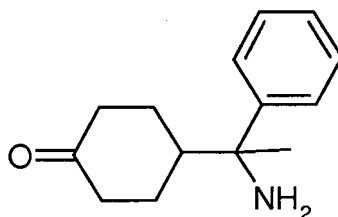
[0311]



[0312] Under argon, phenylmagnesium bromide (3M) in diethyl ether (6.7 mL, 20 mmol) was added to a solution of 1,4-dioxo-spiro[4.5]decane-8-carbonitrile (3.34 g, 20 mmol) in diethyl ether (60 mL). The mixture was stirred for 30 minutes. Titanium (IV) isopropoxide (5.7 g, 20 mmol) was then added. After stirring for 5 min, methyl lithium (1.6 M in diethyl ether, 31.2 mL, 50 mmol) was added and the reaction was heated under reflux for 10 hours. After cooling in ice/water the brown mixture was treated cautiously with 2M NaOH solution (30 mL) dropwise (exothermic). The mixture was extracted with t-butyl methyl ether and dried over sodium sulphate. After filtration the organic phase was evaporated to give 5 g of a pale yellow oil, which was used in the next step without further purification. $R_t = 2.10$ min (Method 2). Detected mass: 261.2 ($M+H^+$).

4-(1-Amino-1-phenyl-ethyl)-cyclohexanone (27)

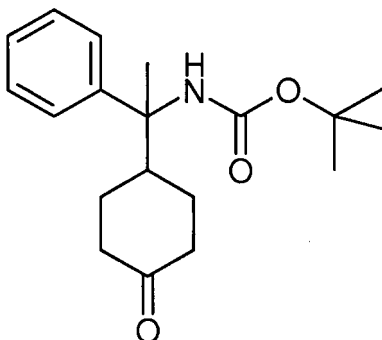
[0313]



[0314] Crude 1-(1,4-dioxo-spiro[4.5]dec-8-yl)-1-phenyl-ethylamine (26, 2.5 g) was dissolved in acetone (40 mL) and treated with 6M aqueous hydrochloric acid (21.1 mL). After 5 hours stirring the mixture was evaporated at less than 20 °C to give a residue which was treated with dichloromethane, washed with saturated sodium bicarbonate solution, dried and filtered to give a solution of crude product which was used immediately. $R_t = 0.7$ min (Method 5). Detected mass: 218.3 ($M+H^+$).

[1-(4-Oxo-cyclohexyl)-1-phenyl-ethyl]-carbamic acid tert-butyl ester (28)

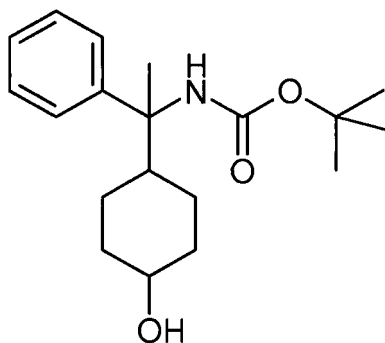
[0315]



[0316] With cooling di-tert.-butyl dicarbonate (3.46 g, 10.6 mmol) and triethylamine (1.47 mL, 10.6 mmol) was added to the crude solution of 4-(1-amino-1-phenyl-ethyl)-cyclohexanone (27) from the previous stage. After stirring overnight, the reaction was worked up by extraction with dichloromethane, washing with 1 M NaOH solution and then with 0.05M aqueous hydrochloric acid (three times until pH of washings were pH4). After washing the organic phase with brine, it was dried over sodium sulphate, filtered and evaporated to give crude product (28) as a colourless oil which was used without further purification. $R_t = 0.14$ min (Method 5). Detected mass: 318.4 ($M+H^+$)

[1-(4-Hydroxy-cyclohexyl)-1-phenyl-ethyl]-carbamic acid tert-butyl ester (29)

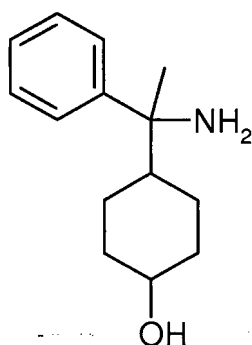
[0317]



[0318] [1-(4-Oxo-cyclohexyl)-1-phenyl-ethyl]-carbamic acid tert-butyl ester (28) from the previous stage (2.7 g) was dissolved in THF (60 mL) and cooled to -70°C . Sodium borohydride was added (356 mg) and the reaction mixture stirred overnight with gradual warming to room temperature. Water was added and the solution extracted with t-butylmethyl ether. The organic phase was washed with brine and dried over sodium sulphate. Evaporation gave 1.24 g of a white foam as crude product. $R_t = 1.41$ min (Method 5). Detected mass: 246.3 ($\text{M}-\text{C}_4\text{H}_8-\text{H}_2\text{O}+\text{H}^+$).

4-(1-Amino-1-phenyl-ethyl)-cyclohexanol (30)

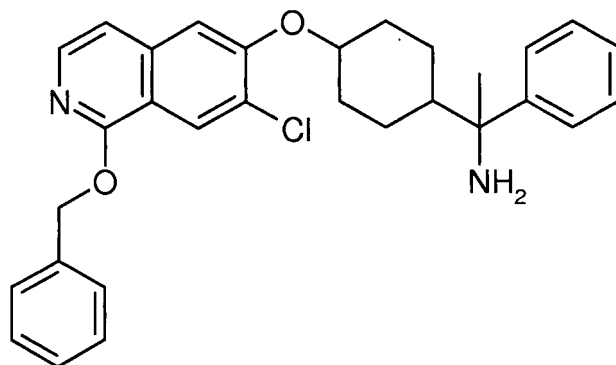
[0319]



[0320] Trifluoroacetic acid (8 mL) was added to a solution of [1-(4-hydroxy-cyclohexyl)-1-phenyl-ethyl]-carbamic acid tert-butyl ester (29) in dichloromethane (75 mL) from the previous stage. After stirring for 4 hours the reaction mixture was worked up by adding 2M aqueous hydrochloric acid (39 mL), followed by evaporation. Freeze drying overnight gave a pale brown semi-solid residue. This was treated with a mixture of water and acetonitrile. After freeze drying again 1.24 g of crude product as the hydrochloride was obtained which was used in the next stage without further purification. $R_t = 0.58$ min (Method 5). Detected mass: 185.15 ($\text{M}-\text{NH}_3-\text{H}_2\text{O}+\text{H}^+$).

1-[4-(1-Benzyloxy-7-chloro-isoquinolin-6-yloxy)-cyclohexyl]-1-phenyl-ethylamine (31)

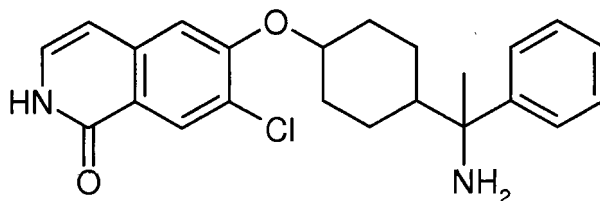
[0321]



[0322] 4-(1-Amino-1-phenyl-ethyl)-cyclohexanol (30, 404 mg, 1.6 mmol) was evaporated twice to dryness from toluene. The residue was dissolved in dimethylacetamide (3 mL) and the solution added dropwise to a suspension of sodium hydride (114 mg, 4.1 mmol, 60% in mineral oil) in dimethyl acetamide (8 mL) under argon. After stirring for 1 hour, a solution of 1-benzyloxy-7-chloro-6-fluoroquinoline (38, 0.31 g, 1.09 mmol) in dimethylacetamide (6 mL) was added dropwise and the mixture stirred overnight. Then mixture was then heated and stirred at 60 °C for 1 hour before cooling and addition of water (30 mL) to quench the reaction. The product was isolated by extraction with dichloromethane/isopropanol (3:1) and evaporation of the organic phase under reduced pressure. Purification by column chromatography (silica gel, 2 % methanol in dichloromethane) gave the desired product (67 mg) as a colourless solid. $R_t = 4.3$ min (Method 3). Detected mass: 487.3 ($M+H^+$).

Example 34: 6-[4-(1-Amino-1-phenyl-ethyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one

[0323]

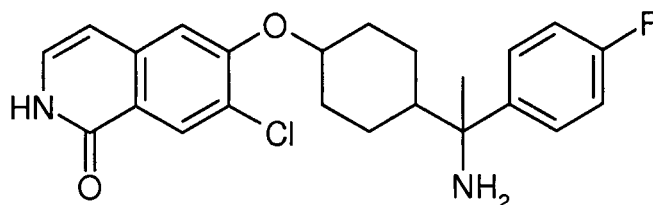


[0324] Hydrochloric acid (6.6 mL of a 2M aqueous solution) was added to a solution of 1-[4-(1-benzyloxy-7-chloro-isoquinolin-6-yloxy)-cyclohexyl]-1-phenyl-ethylamine (31, 67mg, 0.14 mmol) in isopropanol (7 mL). The reaction mixture was stirred overnight. Isopropanol was removed under reduced pressure and the remaining aqueous solution freeze dried to give crude product as an amorphous powder.

This was treated twice with acetonitrile/water and freeze dried to give 57 mg of the desired product as a colourless hydrochloride salt. $R_t = 2.83$ min (Method 3). Detected mass: 380.3 ($M-NH_3+H^+$).

Example 116: 6-[4-[1-Amino-1-(4-fluoro-phenyl)-ethyl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one (Isomer 1)

[0325]



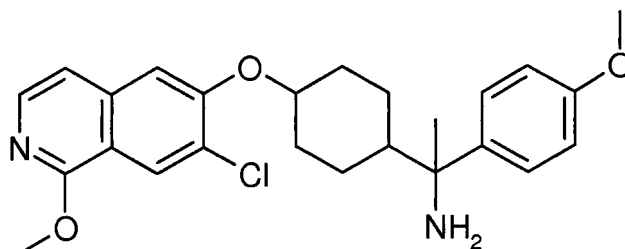
[0326] 6-[4-[1-Amino-1-(4-fluoro-phenyl)-ethyl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one (Example 116) was obtained by the same procedure described for the synthesis of Example 34 using 1-benzyloxy-7-chloro-6-fluoroquinoline (38) and 4-[amino-4-fluorophenyl-methyl]-cyclohexanol (prepared from 1,4-dioxo-spiro[4.5]decane-8-carbonitrile, 4-fluorophenyl-magnesium bromide and methyl lithium analogously to 30). $R_t = 1.74$ min (Method 20). Detected mass:

398.2 (M-NH₃+H⁺).

Example 117: 6-{4-[1-Amino-1-(4-methoxy-phenyl)-ethyl]-cyclohexyloxy}-7-chloro-2H-isoquinolin-1-one

a) 1-[4-(7-chloro-1-methoxyisoquinolin-6-yloxy)-cyclohexyl]-1-(4-methoxyphenyl)-ethylamine (109)

[0327]

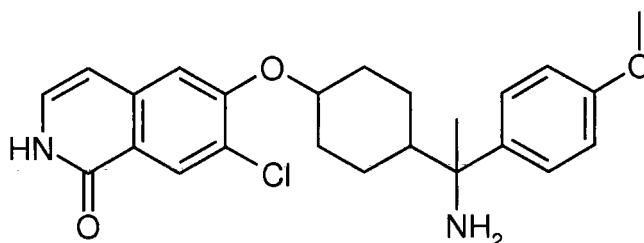


[0328] 4-[1-Amino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol (prepared as described for the synthesis of 30, 400 mg, 1.4 mmol) was evaporated twice to dryness from toluene. The residue was dissolved in dimethylacetamide (3 mL) and the solution added dropwise to a suspension of sodium hydride (147 mg, 3.7 mmol, 60% in mineral oil) in dimethyl acetamide (6 mL) under argon. After stirring for 1 hour, a solution of 7-chloro-6-fluoro-1-methoxyisoquinoline (0.3 g, 1.4 mmol) in dimethylacetamide (6 mL) was then added dropwise and the mixture stirred overnight. The mixture was then heated and stirred at 60 °C for 1 hour before cooling and addition of water (30 mL) to quench the reaction.

[0329] Product was isolated by extraction with dichloromethane/isopropanol (3:1) and evaporation of the organic phase under reduced pressure. Purification by column chromatography (silica gel, dichloromethane to dichloromethane:methanol = 98:2 to MeOH) gave desired product (30 mg) as a colourless solid. R_t = 3.84 min (Method 3). Detected mass: 441.4 (M+H⁺).

b) 6-{4-[1-Amino-1-(4-methoxy-phenyl)-ethyl]-cyclohexyloxy}-7-chloro-2H-isoquinolin-1-one (Example 117)

[0330]



[0331] Hydrochloric acid (0.4 mL of a 1 M aqueous solution) was added to a solution of 1-[4-(7-chloro-1-methoxyisoquinolin-6-yloxy)-cyclohexyl]-1-(4-methoxyphenyl)-ethylamine (109, 30 mg, 0.07 mmol) in isopropanol (0.4 mL). The reaction mixture was heated in a microwave oven at 100 °C for 30 minutes. Isopropanol was removed under reduced pressure and the remaining aqueous solution freeze dried to give crude product as an amorphous powder. This was treated twice with acetonitrile/water and freeze dried to give 29mg of the desired product Example 117 as a colourless hydrochloride salt. R_t = 2.60 min (Method 2). Detected mass: 410.1 (M-NH₃+H⁺).

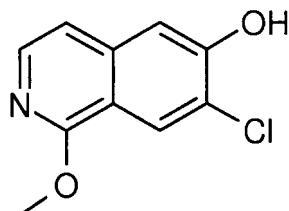
[0332] The following racemic products were obtained by the same procedure described for the synthesis of Example 117 using 7-chloro-6-fluoro-1-methoxyisoquinoline (10) and the corresponding aminoalcohols (prepared from the respective carbonitriles, grignard reagents and methyl or ethyl lithium reagents analogously to 30). One stereoisomer could be isolated (named isomer 1); the relative stereochemistry was not assigned.

Exam ple	Product	Chemical Name	[M+H ⁺]	R _t /[min]	Method
118		6-{4-[1-Amino-1-cyclopentylethyl]-cyclohexyloxy}-7-chloro-2H-isoquinolin-1-one	389.5	3.10	3
119		6-{4-[1-Amino-1-ethyl-propyl]-cyclohexyloxy}-7-chloro-2H-isoquinolin-1-one	363.2	1.71	12
120		6-{4-[1-Amino-1-cyclopropylethyl]-cyclohexyloxy}-7-chloro-2H-isoquinolin-1-one	361.2	1.98	13
121		6-{4-[1-Amino-1-n-propylethyl]-cyclohexyloxy}-7-chloro-2H-isoquinolin-1-one	363.2	1.77	12

Example 122: 6-{4-[1-Amino-1-ethyl-propyl]-cyclohexyloxy}-7-chloro-2H-isoquinolin-1-one (Isomer 2)

a) 7-chloro-6-hydroxy-1-methoxyisoquinoline (110)

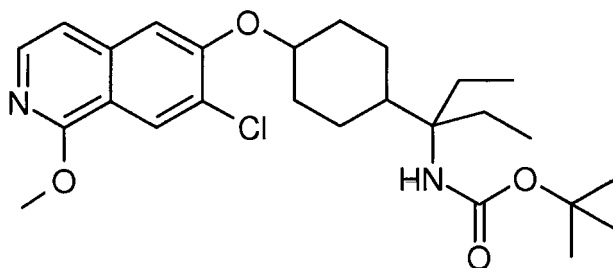
[0333]



[0334] A solution of sodium trimethylsilanoate (149.2 mL, 1 M in THF) was added to a solution of 7-chloro-6-fluoro-1-methoxyisoquinoline (10, 10g, 47.2 mmol) in DMA (200 mL) under argon. After stirring at 60 °C for 24 hours, the solution was evaporated under reduced pressure and then freeze dried to give crude product (20.4 g). This was dissolved in water and the pH adjusted to pH=6.5. A light brown precipitate was collected by filtration and purified by reverse phase chromatography (0 to 4 minutes, 15% acetonitrile/water, 4 to 24 minutes 15 to 90% acetonitrile/water and then 100% acetonitrile) to give 7g of the desired product. R_t = 2.60 min (Method 2). Detected mass: 210.0 (M+H⁺).

b) 1-(4-[7-Chloro-1-methoxyisoquinolin-6yloxy-cyclohexyl]-1-ethyl-propyl)-carbamic acid tert-butyl ester (111)

[0335]

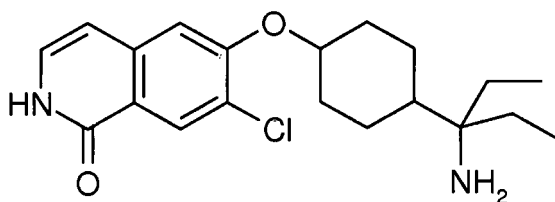


[0336] [1-(4-Hydroxycyclohexyl)-1-ethyl-propyl]-carbamic acid tert-butyl ester (from the preparation of 119) was dried by evaporating twice from toluene. The dried material was dissolved in dry THF (2.5 mL) and triphenylphosphine (0.63 g, 2.42 mmol), and 7-chloro-6-hydroxy-1-methoxyisoquinoline (110, 0.39 g, 1.86 mmol) added. Then Hunig's base (0.24 g, 0.32 mL, 1.86 mmol) was added. The reaction mixture was cooled to 0 °C and DEAD (0.49 g, 434 μl, 2.79 mmol) added dropwise over 1 hour. The reaction mixture was warmed to 25 °C and stirred overnight.

The reaction mixture was taken up in dichloromethane, washed twice with aqueous 2M NaOH solution and once with brine. Drying over sodium sulphate followed by filtration and evaporation gave 1.7 g of crude product which was purified by stirring three times with 5% ethyl acetate/95% heptane. Combined organic extracts were evaporated to give a brown residue which was purified by chromatography on silica gel. Elution with heptane/ethyl acetate (95:5) gave 113 mg of desired compound. R_t = 1.54 min (Method 11). Detected mass: 476.2 (M+H⁺).

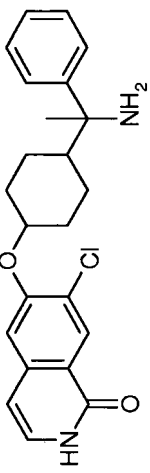
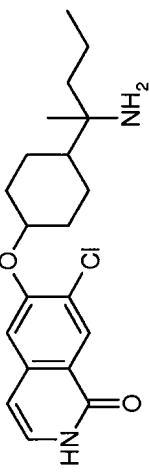
c) 6-{4-[1-Amino-1-ethyl-propyl]-cyclohexyloxy}-7-chloro-2H-isoquinolin-1-one, isomer 2 (Example 122)

[0337]



[0338] 1-(4-[7-Chloro-1-methoxyisoquinolin-6-yloxy-cyclohexyl]-1-ethyl-propyl)-carbamic acid tert-butyl ester (111, 113 mg, 0.24 mmol) was dissolved in isopropanol (1.5 mL) and treated with hydrochloric acid (1 M, 1.5 mL). The reaction mixture was heated in a microwave oven at 100 °C for 30 minutes. Evaporation gave crude product, which was treated twice with acetonitrile/water and freeze dried to give 63 mg of the desired product as a colourless hydrochloride salt. R_t = 2.45 min (Method 2). Detected mass: 363.3 (M+H⁺).

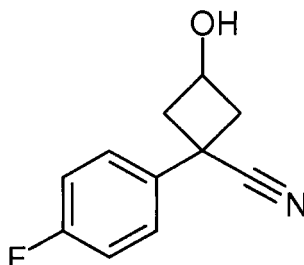
[0339] The following two racemic products were obtained by the same procedure described for the synthesis of Example 122 using 7-chloro-6-hydroxy-1-methoxyisoquinoline (110) and the corresponding 1-(4-hydroxycyclohexyl)-1-ethyl]-carbamic acid tert-butyl ester (prepared analogously to 30). The isolated products are different stereoisomers as compared to Example 34 and Example 121, therefore named "isomer 2", their relative stereochemistry, however, was not assigned.

Example	Product	Chemical Name	[M+H ⁺]	R _f [min]	Method
123	 <p>Isomer 2</p>	6-{4-[1-Amino-1-phenyl-ethyl]-cyclohexyloxy}-7-chloro-2H-isoquinolin-1-one	397.12	1.74	12
124	 <p>Isomer 2</p>	6-{4-[1-Amino-1-methyl-n-butyl]-cyclohexyloxy}-7-chloro-2H-isoquinolin-1-one	363.2	1.76	21

Example 125 and 126: 6-[3-(1-Amino-propyl)-3-(4-fluoro-phenyl)-cyclobutyloxy]-7-chloro-2H-isoquinolin-1-one

a) 3-Cyano-3-(4-fluorophenyl)cyclobutan-1-ol (112)

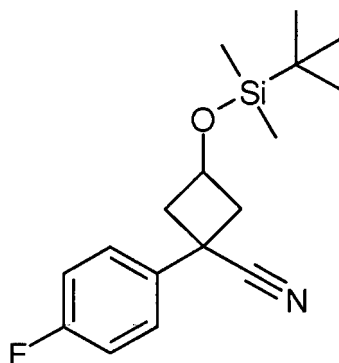
[0340]



[0341] Methyl lithium-lithium bromide complex (123 mL, 185 mmol) was added dropwise to a solution of 4-fluoroacetonitrile (22 mL, 25 g, 185 mmol) in THF (550 mL) at -70 °C. After stirring for 1 hour at -70 °C, a solution of epibromhydrin (15.8 mL, 25.3 g, 185 mmol) in THF (125 mL) was added dropwise. The reaction mixture was stirred for a further hour. Then, at -70 °C, methyl magnesium iodide in ether (3M, 61.7 mL, 185 mmol) was added dropwise and the reaction mixture allowed to warm up gently to room temperature with stirring overnight. The reaction mixture was then cooled in an ice bath and dropwise water (30 mL) and then hydrochloric acid (5M) were added. The acidic solution was saturated with sodium chloride and extracted with methyl t-butyl ether. The organic phase was then washed with sodium thiosulphate solution and brine. After drying over sodium sulphate, followed by filtration, the solvent was removed under reduced pressure to give crude product (33.5 g) as an orange oil. The compound was purified by chromatography on silica gel, elution with heptane/ethyl acetate gave 19.8 g of the desired compound. $R_t = 3.33$ min (Method 3). Detected mass: 192.1 (M+H⁺).

b) 3-Cyano-3-(4-fluorophenyl)cyclobutan-1-yl t-butyldimethylsilyl ether (113)

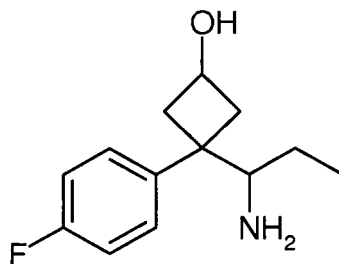
[0342]



[0343] 3-cyano-3-(4-fluorophenyl)cyclobutan-1-ol (112, 19.8 g, 103.6 mmol) was dissolved in dichloromethane (200 mL) under argon, then 2,6-lutidine (27.78 g, 30.1 mL, 259 mmol) was added and the solution cooled to 0 °C. tert-Butyldimethylsilyl trifluoromethanesulphonate (32.9 g, 28.6 mL, 124.3 mmol) was added dropwise and the stirred reaction mixture was then allowed to warm up to room temperature overnight. The reaction mixture was washed successively with water, hydrochloric acid (0.1 M), saturated sodium bicarbonate solution and brine before being dried over sodium sulphate. Filtration and evaporation gave 32.9 g of a yellow oil which was used in the next step without further purification. $R_t = 1.30$ min (Method 18). Detected mass: 306.3 (M+H⁺).

c) 1-(1-Aminopropyl)-1-(4-fluorophenyl)cyclobutan-3-ol (114)

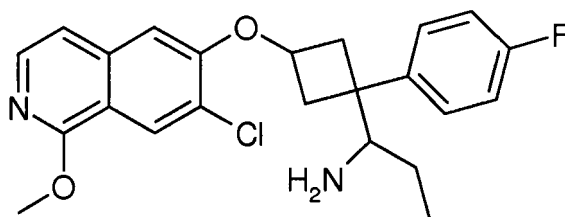
[0344]



[0345] 3-cyano-3-(4-fluorophenyl)cyclobutan-1-yl-t-butyldimethylsilyl ether (113, 1.55 g, 5.1 mmol) was dissolved in toluene (4 mL) and ethyl magnesium bromide (3.4 mL, 10.2 mmol, 3M in ether) added dropwise. The reaction mixture was then stirred for 30 minutes at 90 °C. After cooling to 0 °C, the reaction was quenched by addition of methanol (20 mL) followed by addition of sodium borohydride (384 mg, 10.2 mmol). After stirring overnight dilute sodium hydroxide was added (50 mL, 1 M aqueous solution) and the mixture extracted with methyl-tert-butyl ether. The organic phase was stirred with hydrochloric acid (2N, 100 mL) for 4 hours. The aqueous layer was then washed with methyl-tert butyl ether before being made basic with sodium hydroxide solution (5M) and extracted with dichloromethane/isopropanol (3/1). Evaporation of the organic layer gave 900 mg of (114) as a yellow oil. R_t = 1.04 min (Method 10). Detected mass: 224.2 (M+H⁺).

d) 1-[3-(7-Chloro-1-methoxyisoquinolin-6-yloxy)-cyclobutyl]-1-(4-fluorophenyl)-propylamine (115 and 116)

[0346]



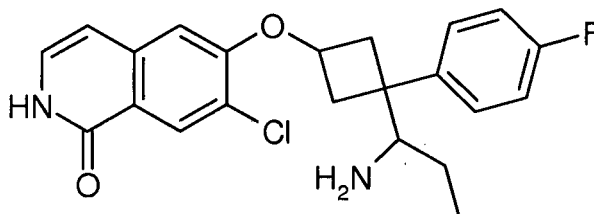
[0347] 1-[3-(7-chloro-1-methoxyisoquinolin-6-yloxy)-cyclobutyl]-1-(4-fluorophenyl)-propylamine (2 isomeric mixtures) were prepared from 1-(1-aminopropyl)-1-(4-fluorophenyl)cyclobutan-3-ol (114) and 7-chloro-6-fluoro-1-methoxyisoquinoline (10) as described for (109). The two stereoisomers could be separated by silica gel chromatography, relative stereochemistry was not assigned.

115: R_t = 1.50 min (Method 10). Detected mass: 415.2 (M+H⁺)

116: R_t = 1.55 min (Method 10). Detected mass: 415.2 (M+H⁺)

e) 6-[3-(1-Amino-propyl)-3-(4-fluoro-phenyl)-cyclobutyloxy]-7-chloro-2H-isoquinolin-1-one (Example 125 and 126)

[0348]



[0349] 6-[3-(1-Amino-propyl)-3-(4-fluorophenyl)-cyclobutyloxy]-7-chloro-2H-isoquinolin-1-one (Example 125 and 126) were prepared from 1-[3-(7-chloro-1-methoxyisoquinolin-6-yloxy)-cyclobutyl]-1-(4-fluorophenyl)-propylamines 115 and 116 as described for Example 117.

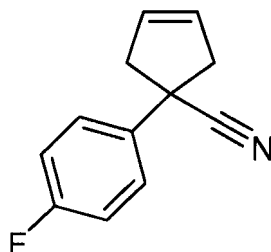
Example 125: R_t = 0.94 min (Method 11). Detected mass: 401.1 (M+H⁺).

Example 126: R_t = 1.34 min (Method 10). Detected mass: 401.1 (M+H⁺).

Example 127: 6-[3-(1-Amino-propyl)-3-(4-fluoro-phenyl)-cyclopentyloxy]-7-chloro-2H-isoquinolin-1-one

a) 1-cyano-1-(4-fluorophenyl)cyclopent-3-ene (117)

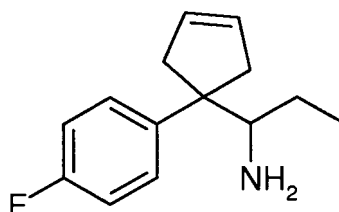
[0350]



[0351] Sodium hydride (14.4 g, 0.36 mol, 60% in oil) was added to ice cooled DMSO (500 mL) under argon and stirred for 10 minutes. 4-Fluoroacetonitrile (22.4 g, 0.16 mol) was dissolved in DMSO (200 mL) and then added over 15 minutes to the stirred, cooled sodium hydride mixture. After dropwise addition of cis-1,4-dichlorobutene (17.7 g, 14.9 mL) the mixture was allowed to warm to room temperature and was then stirred overnight. The reaction was quenched by gentle addition to 1000 mL ice cold water and followed by extraction with dichloromethane. Evaporation gave crude product which was taken up in heptane/ethyl acetate (1/1) and washed with water three times. The organic phase was dried over sodium sulphate, filtered and evaporated to give 33.7 g red oil. This was purified by chromatography on silica gel, elution with heptane/ethyl acetate (1/2) gave 10.1 g of desired compound 117.

b) 1-(1-aminopropyl)-1-(4-fluorophenyl)cyclopent-3-ene (118)

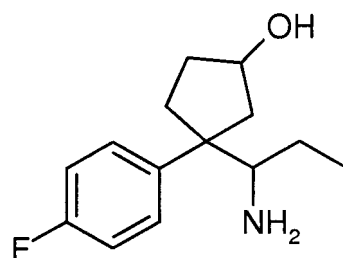
[0352]



[0353] 1-cyano-1-(4-fluorophenyl)cyclopent-3-ene (117, 1.4 g, 7.48 mmol) was dissolved in toluene (3.5 mL) and ethyl magnesium bromide (5 mL, 15 mmol, 3M in ether) added. After stirring for 2.5 hours, the reaction mixture was added dropwise to ice cold methanol (50 mL), followed by sodium borohydride (560 mg, 15 mmol). The mixture was warmed to room temperature and stirred overnight. The white suspension was treated with sodium hydroxide solution (aq, 1M, 125 mL) and then extracted with dichloromethane/isopropanol (3/1). The organic phase was washed with brine, dried over sodium sulphate and evaporated to give 1.2 g of a yellow oil. This was taken up in dichloromethane and extracted twice with dilute hydrochloric acid (2M). The combined aqueous layers were made basic with aqueous sodium hydroxide solution (5M) and reextracted with dichloromethane/isopropanol (3/1). Drying over sodium sulphate and evaporation gave 348 mg of the desired product $R_t = 2.37$ min (Method 2). Detected mass: 220.1 (M+H⁺).

c) 1-(1-aminopropyl)-1-(4-fluorophenyl)cyclopentan-3-ol (119)

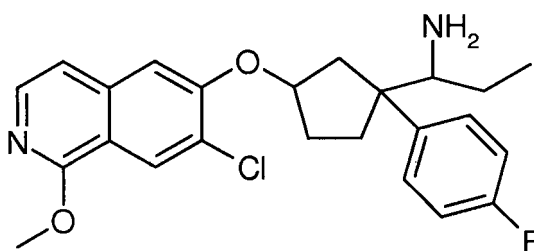
[0354]



[0355] 1-(1-aminopropyl)-1-(4-fluorophenyl)cyclopent-3-ene (118, 348 mg, 1.6 mmol) was dissolved in THF at 0 °C under argon. Borane (1.75 mL, 1.75 mmol, 1 M in THF) was added dropwise over 10 minutes. The reaction mixture was allowed to warm to room temperature before stirring overnight. After cooling to 0 °C, water was added (4 mL), followed by hydrogen peroxide (0.61 mL, 30% solution in water) and sodium hydroxide solution (1.75 mL, 1 M aqueous solution). After stirring for 5 minutes the mixture was extracted with ethyl acetate, dried over sodium sulphate and evaporated to give 458 mg of desired product, which was stirred for 15 minutes with dilute hydrochloric acid (10 mL, 2M aqueous solution). Evaporation, followed by freeze drying gave 514 mg of the desired product as mixture of four stereoisomers as a colourless hydrochloride salt. $R_t = 1.83, 1.99, 2.36, 2.86$ min (Method 2). Detected mass: 203.1 ($M-NH_3-H_2O+H^+$).

d) 1-[3-(7-chloro-1-methoxyisoquinolin-6-yloxy)-cyclopentyl]-1-(4-fluorophenyl)-propylamine (120)

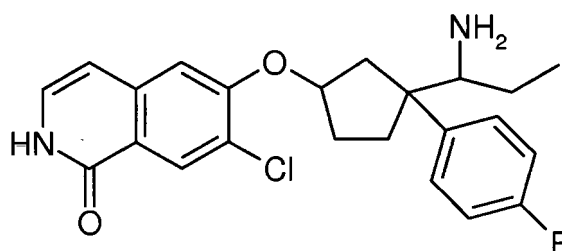
[0356]



[0357] 1-[3-(7-chloro-1-methoxyisoquinolin-6-yloxy)-cyclopentyl]-1-(4-fluorophenyl)-propylamine (120) was prepared from 1-(1-aminopropyl)-1-(4-fluorophenyl)cyclopentan-3-ol (119) and 7-chloro-6-fluoro-1-methoxyisoquinoline (10) as described for 109. $R_t = 1.11$ min (Method 11). Detected mass: 429.3 ($M+H^+$). The product was obtained as a mixture of isomers, their relative stereochemistry was not assigned.

e) 6-[3-(1-Amino-propyl)-3-(4-fluorophenyl)-cyclopentyl]-7-chloro-2H-isoquinolin-1-one (Example 127)

[0358]



[0359] 6-[3-(1-Amino-propyl)-3-(4-fluorophenyl)-cyclopentyl]-7-chloro-2H-isoquinolin-1-one (Example 127) was prepared from 1-[3-(7-chloro-1-methoxyisoquinolin-6-yloxy)-cyclopentyl]-1-(4-fluorophenyl)-propylamine (120) as described for Example 117. The material was obtained as a mixture of stereoisomers, their relative stereochemistry was not assigned. $R_t = 1.34, 1.37$ min (Method 10). Detected mass: 415.1 ($M+H^+$).

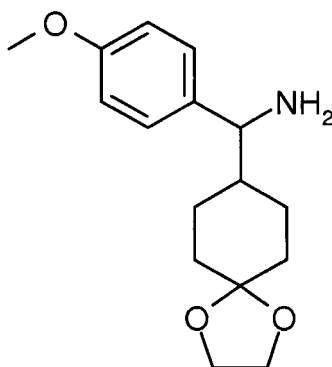
C-(1,4-Dioxo-spiro[4.5]dec-8-yl)-C-(4-methoxy-phenyl)-methylamine (32)

[0360]

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[0361] Under argon, 4-methoxy-phenylmagnesium bromide (0.5M in THF, 24 mL, 12 mmol) was added to a solution of 1,4-dioxo-spiro[4.5]decane-8-carbonitrile (1.0 g, 6 mmol) in THF (100 mL). The mixture was stirred under reflux for 16 hours. The reaction mixture was then cooled to 0 °C. Saturated sodium sulphate solution was added dropwise until no more precipitate formed. The precipitate was removed by filtration and washed with THF. The combined organic phases were stirred with sodium borohydride (452 mg, 12 mmol) overnight at 25 °C. The reaction mixture was then diluted with t-butyl methyl ether (100 mL) and treated with 0.05M aqueous hydrochloric acid (three times with 100 mL). The combined aqueous phases were adjusted to alkaline pH with a 6M aqueous sodium hydroxide solution with cooling, before extraction with dichloromethane gave a solution of the desired product which was used directly in the next stage. $R_t = 0.74$ min (Method 5). Detected mass: 278.2 (M+H⁺).

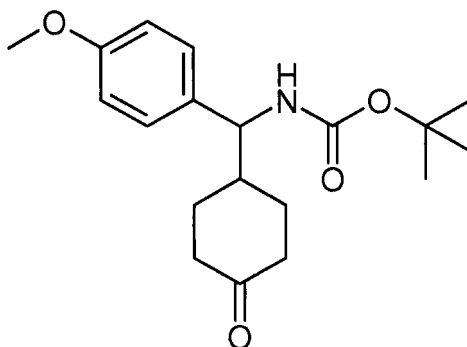
[(4-Methoxy-phenyl)-(4-oxo-cyclohexyl)-methyl]-carbamic acid tert-butyl ester (33)

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[0362]

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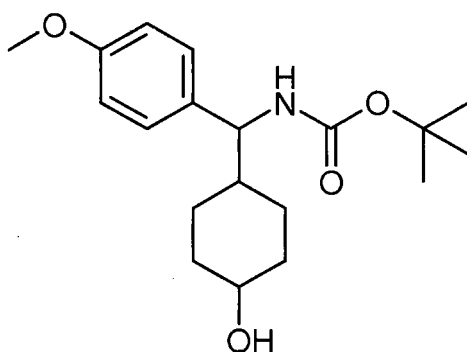
50

[0363] With cooling di-tert.-butyl dicarbonate (1.31 g, 6 mmol) and triethylamine (0.83 mL, 6 mmol) were added to the crude solution of C-(1,4-dioxo-spiro[4.5]dec-8-yl)-C-(4-methoxy-phenyl)-methylamine (32) from the previous stage. After stirring overnight, the reaction was worked up by extraction with dichloromethane and washing with 1 M HCl. The aqueous layer was treated with 1 M NaOH solution to basic pH and then extracted with dichloromethane. After washing the combined organic phase with brine, and drying over sodium sulphate, the organic phase was evaporated to give crude product which was chromatographed on silica gel. Elution with ethyl acetate/hexane (30/70) gave 110 mg of the desired product. $R_t = 4.42$ min (Method 6). Detected mass: 278.1 (M-isobutene+H⁺).

[(4-Hydroxy-cyclohexyl)-(4-methoxy-phenyl)-methyl]-carbamic acid tert-butyl ester (34)

55

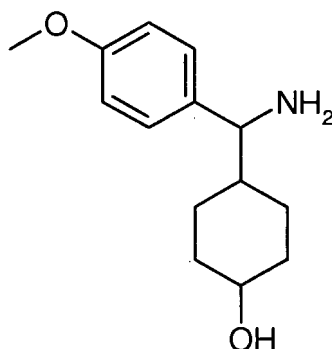
[0364]



[0365] Sodium borohydride (12 mg, 0.34 mmol) and 2 drops methanol were added to a solution of [(4-methoxyphenyl)-(4-oxo-cyclohexyl)-methyl]-carbamic acid tert-butyl ester (33, 110 mg) in THF (5 mL). After stirring for 7 hours the reaction was worked up by washing the solution with saturated sodium bicarbonate solution and brine. After drying the organic phase over sodium sulphate, followed by filtration, evaporation gave 101 mg of the desired cis/trans isomer mixture (34) as a colourless solid, which was used directly in the next stage. $R_t = 1.36, 1.39$ min (Method 5). Detected mass: 219.2 ($M - C_4H_8 - CO_2 - H_2O^+$).

4-[Amino-(4-methoxy-phenyl)-methyl]-cyclohexanol (35)

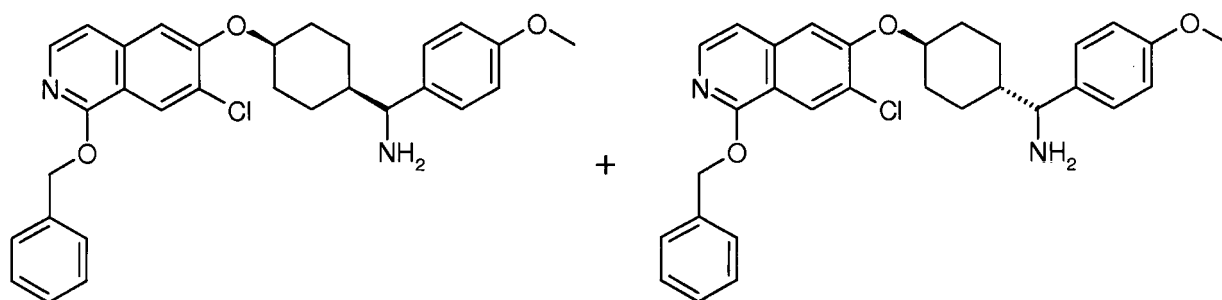
[0366]



[0367] Trifluoroacetic acid (0.31 mL) was added to a solution of [(4-hydroxy-cyclohexyl)-(4-methoxy-phenyl)-methyl]-carbamic acid tert-butyl ester (34, 101 mg) in dichloromethane (6 mL). After stirring for 2 hours, 2M hydrochloric acid (3 mL) was added. Evaporation gave crude product as a colourless solid. Water and acetonitrile were added and the mixture was concentrated and then freeze dried to give 83 mg of 4-[amino-(4-methoxy-phenyl)-methyl]-cyclohexanol (35) as the hydrochloride salt. $R_t = 0.71$ min (Method 5). Detected mass: 219.2 ($M - NH_2^+$).

C-[4-(1-Benzyloxy-7-chloro-isoquinolin-6-yloxy)-cyclohexyl]-C-(4-methoxy-phenyl)-methylamine (36 and 37).

[0368]



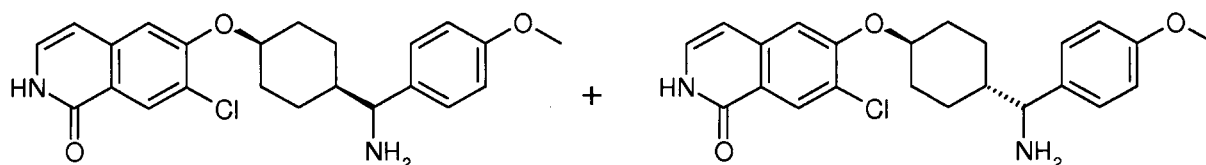
[0369] 4-[Amino-(4-methoxy-phenyl)-methyl]-cyclohexanol (35, 83 mg, 0.3 mmol) was evaporated twice to dryness from toluene. The residue was dissolved in dimethylacetamide (1 mL) and the solution added dropwise to a suspension of sodium hydride, (37 mg, 0.92 mmol, 60% in mineral oil) in dimethyl acetamide (2 mL) under argon. After stirring for 1 hour a solution of 1-benzyloxy-7-chloro-6-fluoroquinoline (38, 62 mg, 0.21 mmol) in dimethylacetamide (2 mL) was then added dropwise and the mixture stirred overnight. Then mixture was then treated with water (6 mL) to quench the reaction. Product was isolated by extraction with dichloromethane/isopropanol(3:1) and the crude product was then obtained by evaporation of the organic phase under reduced pressure. Purification by column chromatography (silica gel, 5% methanol in dichloromethane) gave 40 mg of the earlier eluting isomer 1 (36) and 40 mg of the later eluting isomer 2 (37), both as colourless solids. The relative stereochemistry was not assigned.

36: $R_t = 1.46$ min (Method 5). Detected mass: 503.2 ($M+H^+$).

37: $R_t = 1.51$ min (Method 5). Detected mass: 503.2 ($M+H^+$).

Example 35 and Example 36: 6-{4-[Amino-(4-methoxy-phenyl)-methyl]-cyclohexyloxy}-7-chloro-2H-isoquinolin-1-one

[0370]



[0371] A 2M aqueous solution of hydrochloric acid (3.8 mL) was added to a solution of C-[4-(1-benzyloxy-7-chloro-isoquinolin-6-yloxy)-cyclohexyl]-C-(4-methoxy-phenyl)-methylamine (36, 40 mg, 0.08 mmol) in isopropanol (4 mL). The reaction mixture was stirred overnight. Isopropanol was removed under reduced pressure and the remaining aqueous solution freeze dried to give crude product as an amorphous powder. This was treated twice with acetonitrile/water and freeze dried to give the desired product as a colourless hydrochloride salt. The relative stereochemistry was not assigned.

Example 35: $R_t = 2.56$ min (Method 1). Detected mass: 396.2 ($M-NH_2^+$)

Example 36 was synthesized analogously starting from 37: $R_t = 2.86$ min (Method 1).

Detected mass: 396.2 ($M-NH_3+H^+$)

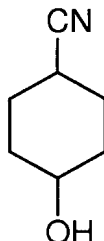
[0372] The following four products were obtained by the same procedure described for the synthesis of example 35 and example 36 using 1-benzyloxy-7-chloro-6-fluoroisoquinoline and the corresponding 4-[amino-phenyl-methyl]-cyclohexanols, using the respective phenyl Grignard reagents and 1,4-dioxo-spiro[4.5]decane-8-carbonitriles.

Ex. No.	Product	Chemical Name	[M+H ⁺]	Isomer	R _f [min]	Method
37		6-[4-(Amino-(4-fluoro-phenyl)-methyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	401.2	1	2.61	1
38		6-[4-(Amino-p-tolyl-methyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	397.2	1	2.69	1
39		6-[4-(Amino-p-tolyl-methyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	397.0	2	2.63	1
40		6-[4-(Amino-phenyl-methyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	383.2	1	2.51	1

[0373] Alternative synthesis of Example 40: 6-[4-(Amino-phenyl-methyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one

a) 4-Hydroxy-cyclohexanecarbonitrile (121)

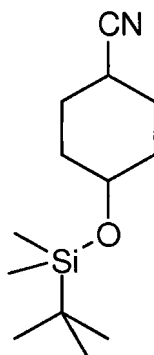
[0374]



[0375] A solution of 10.0 g (59.8 mmol) of 4-cyanocyclohexanone cyclic ethylene acetal in a mixture of 80 mL of acetic acid and 20 mL of water was heated in the microwave oven at 130 °C for 20 min. The mixture was cooled to room temperature and slowly poured onto 2.2 L of cold saturated aqueous sodium bicarbonate solution. The mixture was extracted twice with dichloromethane, the organic phase was dried over magnesium sulphate, filtered, 100 mL of ethanol were added and the dichloromethane was removed *in vacuo*. To the solution were then added 2.0 g (52.9 mmol) of sodium borohydride and the mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, and extracted twice with dichloromethane. The combined organic layer was concentrated *in vacuo* to give 6.4 g of 4-hydroxycyclohexanecarbonitrile as a mixture of cis/trans isomers in a purity sufficient for further conversion. $R_t = 0.14$ min (Method 18). Detected mass: 126.1 ($M+H^+$).

b) 4-(tert-Butyl-dimethyl-silanyloxy)-cyclohexane-carbonitrile (122)

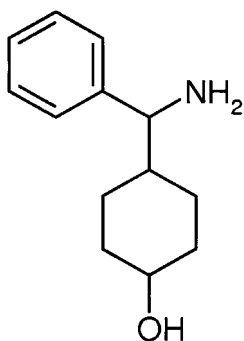
[0376]



[0377] 6.4 g (51.1 mmol) of 4-hydroxy-cyclohexanecarbonitrile (121) were dissolved in 120 mL of dichloromethane, cooled to 0 °C and 14.9 mL (13.7 g, 128 mmol) of 2,6-lutidine and 15.4 mL (14.9 g, 56.2 mmol) of tert-butyldimethylsilyltrifluoromethanesulfonate were added. The reaction mixture was stirred for 16h at room temperature, then additional 5.0 mL of tert-butyldimethylsilyltrifluoromethanesulfonate were added and stirring continued for 1 h. The reaction mixture was diluted with 100 mL of dichloromethane and washed with 100 mL of water, 80 mL of saturated aqueous sodium bicarbonate solution and 50 mL of brine. The organic phase was dried over magnesium sulphate, filtered, concentrated *in vacuo* and purified by silica gel chromatography (heptanes:ethyl acetate) to give 9.76 g of the desired product. $R_t = 0.95$ min (Method 18). Detected mass: 240.1 ($M+H^+$).

c) 4-(Amino-phenyl-methyl)-cyclohexanol (123)

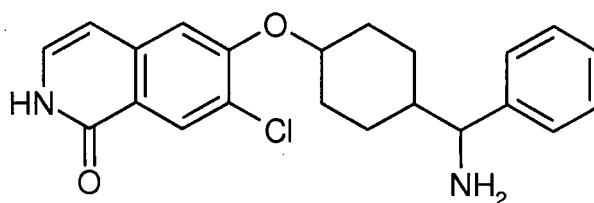
[0378]



[0379] 417 mg of 4-(Amino-phenyl-methyl)-cyclohexanol (123) as mixture of diastereoisomers was synthesized using the sequence described for the synthesis of 93, starting from 700 mg of 4-(tert-butyl-dimethyl-silanyloxy)-cyclohexane-carbonitrile (122) and 2.09 mL (5.85 mmol) of phenylmagnesium bromide. $R_t = 0.43$ min (Method 18). Detected mass: 206.1 ($M+H^+$).

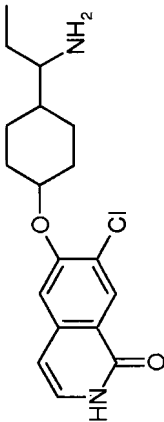
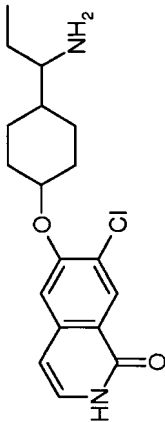
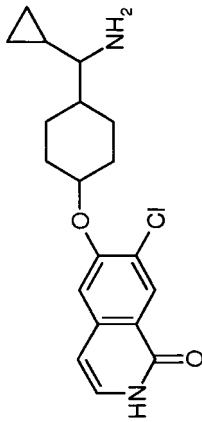
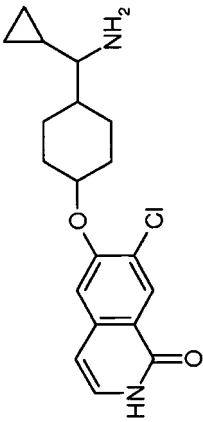
d) 6-[4-(amino-phenyl-methyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one (Example 40)

[0380]



[0381] Example 40 was synthesized using the reaction sequence as described for the synthesis of Example 1. 240 mg of 4-(amino-phenyl-methyl)-cyclohexanol (123) and 272 mg of 7-chloro-6-fluoro-1-methoxy-isoquinoline (10) were used to give 51 mg of Example 40 as its hydrochloride. $R_t = 1.34$ min (Method 10). Detected mass: 383.1 ($M+H^+$). 28 mg of the other isomer of 4-(amino-phenyl-methyl)-cyclohexanol (Example 128) were also isolated as its hydrochloride. $R_t = 1.31$ min (Method 10). Detected mass: 383.1 ($M+H^+$). Separation of the two isomers was accomplished by silica gel chromatography after coupling of aminoalcohol 123 and 10. Relative stereochemistry was not assigned.

[0382] The following examples were obtained in a similar fashion as described for the alternative preparation of Example 40, using the corresponding isoquinolines and 4-(amino-methyl)-cyclohexanols (prepared following the sequence described for the synthesis of 123) as starting materials:

Ex.-No.	Product	Chemical Name	[M+H ⁺]	Isomer	R _t [min]	Method
129		6-[4-(1-Aminopropyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	335.1	1	1.24	10
130		6-[4-(1-Aminopropyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	335.1	2	1.19	10
131		6-[4-(Aminocyclopropylmethyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	347.2	1	2.38	2
132		6-[4-(Aminocyclopropylmethyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one	347.2	2	2.36	2

[0383] The following racemates were separated by HPLC, using a chiral column. Absolute stereochemistry was not determined, the earlier eluting enantiomer was designated to be enantiomer one. In case of Example 41 and Example 42, enantiomeric separation was performed on stage of the racemic O-benzyl protected precursor (1-[trans-4-(1-benzyloxy-7-chloro-isoquinolin-6-yloxy)-1-phenyl-cyclohexyl]-1-phenyl-methylamine) and the final products were liberated after separation, using the standard procedure described above. In the case of Example 41 and Example 42, data for retention times is given for said protected compounds.

Example	Racemate	Enantiomer	Method	R _t chiral [min]
41	21	1	B	6.84
42	21	2	B	9.01
43	01	1	A	6.18
44	01	2	A	9.22
45	03	1	A	4.98
46	03	2	A	7.05
47	26	1	A	6.24
48	26	2	A	8.87
49	24	1	A	4.56
50	24	2	A	7.96
51	37	1	C	5.53
52	37	2	C	8.12
53	32	1	A	11.60
54	32	2	A	15.03

[0384] The enantiomers obtained from these examples by separation of the racemate are trans-6-[4-((S)-Amino-phenyl-methyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, trans-6-[4-((R)-Amino-phenyl-methyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, cis-6-[4-((S)-1-Amino-propyl)-4-fluoro-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, cis-6-[4-((R)-1-Amino-propyl)-4-fluoro-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, cis-6-[4-((S)-Amino-cyclopropyl-methyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, cis-6-[4-((R)-Amino-cyclopropyl-methyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, cis-6-[4-((R)-Amino-cyclopropyl-methyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, cis-6-[4-((S)-Amino-cyclopropyl-methyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, cis-6-[4-((S)-1-Amino-ethyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, cis-6-[4-((R)-1-Amino-ethyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, 6-{4-[(S)-Amino-(4-fluoro-phenyl)-methyl]-cyclohexyloxy}-7-chloro-2H-isoquinolin-1-one, 6-{4-[(R)-Amino-(4-fluoro-phenyl)-methyl]-cyclohexyloxy}-7-chloro-2H-isoquinolin-1-one, cis-6-[4-((R)-1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, and cis-6-[4-((S)-1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one. (enantiomers have not been assigned to "Enantiomer 1 or "Enantiomer 2", respectively)

LC/MS-Methods:

Method 1:

[0385]

Stationary phase: Waters XBridge C18
 Gradient: ACN+0.05% TFA : H₂O+0.05% TFA
 5:95(0 min) to 5:95(0.3 min) to 95:5(3.5 min) to 95:5(4 min)
 Flow: 1.3 mL/min

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Method 2:

[0386]

5 Stationary phase: Col YMC Jsphere 33 x 2.1
 Gradient: ACN+0.05% TFA : H₂O+0.05% TFA
 2:98(0 min) to 2:98(1 min) to 95:5(5 min) to 95:5(6.25 min)
 Flow: 1 mL/min

10

Method 3:

[0387]

15 Stationary phase: Waters XBridge C18
 Gradient: ACN+0.1 % FA : H₂O+0.1% FA
 3:97(0 min) to 60:40(3.5 min) to 98:2(4.0 min) to 98:2(5.0 min) to 3:97(5.2 min) to 3:97(6.5 min)
 Flow: 1.3 mL/min

20

Method 4:

[0388]

25 Stationary phase: YMCJsphere H80, 33x2
 Gradient: H₂O+0.1% FA : ACN+0.08% FA
 95:5 (0 min) to 5:95(2.5 min) to 5:95(3 min)
 Flow: 1.3 mL/min

30

Method 5

[0389]

35 Stationary phase: Col YMC Jsphere ODS H80 20 x 2
 Gradient: ACN : H₂O+0.05% TFA
 4:96(0 min) to 95:5(2.0 min) to 95:5(2.4 min)
 Flow: 1 mL/min

40

Method 6:

[0390]

45 Stationary phase: WatersXBridge C18
 Gradient: H₂O+0.1% FA : ACN+0.08% FA
 97:3(0 min) to 40:60(3.5 min) to 2:98(4 min) to 2:98 (5 min) to 97:3(5.2min) to 97:3(6.5min)
 Flow: 1.3 mL/min

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Method 7:

[0391]

55 Stationary phase: Column Acquity BEH C18, 50x2.1 mm, 1.7 μm
 Gradient: H₂O+0.05% TFA : ACN+0.035% TFA
 98:2(0 min) to 0:100(1.6 min) to 0:100(2.1 min) to 98:2(3 min)
 Flow: 1 mL/min

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Method 8:

[0392]

5 Stationary phase: Column Gemini C18, 30x4.6 mm, 3 µm
 Gradient: H₂O+0.1% FA : ACN+0.1% FA
 95:5(0 min) to 0:100(5.5 min) to 0:100(7.5 min)
 Flow: 1 mL/min

10

Method 9:

[0393]

15 Stationary phase: Column Gemini C18, 30x4.6 mm, 3 µm
 Gradient: H₂O+0.1 % FA : ACN+0.1 % FA
 95:5(0 min) to 95:5(1 min) to 0:100(9 min) to 0:100(12 min)
 Flow: 1 mL/min

20

Method 10:

[0394]

25 Stationary phase: Merck Chromolith fast Grad
 Gradient: H₂O+0.05% TFA : ACN+0.035% TFA
 98:2(0 min) to 98:2(0.2 min) to 2:98 (2.4 min) to 2:98 (3.2min) to 98:2(3.3min) to 98:2(4 min)
 Flow: 2 mL/min

30

Method 11:

[0395]

35 Stationary phase: Waters Aquity SDS
 Gradient: H₂O+0.1% FA : ACN+0.08% FA
 95:5(0 min) to 5:95(1.1 min) to 5:95 (1.7 min) to 95:5 (1.8min) to 95:5(2.0min)
 Flow: 0.9 mL/min

40

Method 12:

[0396]

45 Stationary phase: WatersXBridge C18
 Gradient: H₂O+0.05% TFA : ACN+0.05% TFA
 95:5(0 min) to 95:5(0.2 min) to 5:95(2.4 min) to 5:95 (3.5 min) to 95:5(3.6min) to 95:5(4.5min)
 Flow: 1.7 mL/min

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Method 13:

[0397]

55 Stationary phase: WatersXBridge C18
 Gradient: H₂O+0.05% TFA : ACN+0.05% TFA
 95:5(0 min) to 95:5(0.2 min) to 5:95(2.4 min) to 5:95 (3.2 min) to 95:5(3.3min) to 95:5(4.0min)
 Flow: 1.7 mL/min

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Method 14:

[0398]

5 Stationary phase: WatersXBridge C18
 Gradient: H₂O+0.05% TFA : ACN+0.05% TFA
 95:5(0 min) to 95:5(0.1 min) to 5:95(3.3 min) to 95:5(3.85min) to 95:5(4.3min)
 Flow: 1.7 mL/min

10

Method 15:

[0399]

15 Stationary phase: Luna 3 μ C18(2) 10 x 2.0 mm
 Gradient: ACN : H₂O+0.05% TFA
 7:93(0 min) to 95:5(1.2 min) to 95:5(1.4 min)
 Flow: 1.1 mL/min

20

Method 16:

[0400]

25 Stationary phase: Merck Chromolith fast Grad
 Gradient: H₂O+0.05% TFA : ACN+0.05% TFA
 98:2(0 min) to 98:2(0.2 min) to 2:98 (2.4 min) to 2:98 (3.2min) to 98:2(3.3min) to 98:2(4 min)
 Flow: 2.4 mL/min

30

Method 17:

[0401]

35 Stationary phase: Luna 3 μ C18(2) 10 x 2.0 mm (????)
 Gradient: ACN : H₂O+0.05% TFA
 20:80(0 min) to 95:5(0.8 min) to 95:5(1.4 min) to 20:80(1.45 min)
 Flow: 1.1 mL/min

40

Method 18:

[0402]

45 Stationary phase: Luna 3 μ C18(2) 10 x 2.0 mm
 Gradient: ACN : H₂O+0.05% TFA
 7:93(0 min) to 95:5(1.2 min) to 95:5(1.4 min) to 7:93(1.45 min)
 Flow: 1.1 mL/min

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Method 19:

[0403]

55 Stationary phase: Col YMC Jsphere ODS H80 20 x 2
 Gradient: ACN : H₂O+0.05% TFA
 4:96(0 min) to 95:5(2.0 min) to 95:5(2.4 min) to 4:96 (2.45 min)
 Flow: 1 mL/min

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Method 20:

[0404]

5 Stationary phase: WatersXBridge C18, 4.6, 6 x 50 2.5 μ
 Gradient: Water+0.05%TFA:ACN+0.05%TFA
 95:5(0 min) to 5:95(2.6 min) to 5:95(3.0 min) to 95:5(3.10 min) to 95:5 (4 min)
 Flow 1.7 mL/min

10

Method 21:

[0405]

15 Stationary phase: WatersXBridge C18, 4.6, 6 x 50 2.5 μ
 Gradient: Water+0.05%TFA:ACN+0.05%TFA
 95:5(0 min) to 95:5(0.2 min) to 5:95(2.4 min) to 5:95(3.5 min) to 95:5(3.6 min) to 95:5(4.5 min)
 Flow 1.7 mL/min

20

Methods for chiral resolution

Method A:

[0406]

25 Stationary phase: Chiralpak AD-H, 250x4.6 mm
 Eluent: MeOH:iPrOH 2:1 + 0.1% diethylamine
 Flow: 1 mL/min
30 Detection: 249 nM

Method B:

[0407]

35 Stationary phase: Chiralpak AD-H, 250x4.6 mm
 Eluent: Heptane:EtOH:MeOH (5:1:1), column preconditioned with 0.1% diethylamine
 Flow: 1 mL/min
40 Detection: 249 nM

Method C:

[0408]

45 Stationary phase: Chiralpak AD-H, 250 x 4,6mm.
 Eluent: MeOH:EtOH (1:1) + 0.1 % diethylamine.
 Flow: 1 mL/min
50 Detection: 249 nM

Determination of Rho kinase inhibition

[0409] To measure Rho-kinase inhibition, IC₅₀ values were determined according to the following protocol:

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Active human recombinant ROCK II (N-terminal His6-tagged recombinant human ROCK-II residues 11-552) was purchased from Millipore GmbH, Schwalbach, Germany. The peptide substrate, Fluorescein-AKRRRLSSLRA-COOH, was obtained from JPT Peptide Technologies, Berlin, Germany. Adenosine-5'-triphosphate (ATP), bovine

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serum albumine (BSA), dimethylsulphoxide (DMSO), 4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid (Hepes), Brij-35, dithiothreitol (DTT) and Pluronic F-68 were purchased from Sigma-Aldrich, Munich, Germany. Tris(hydroxymethyl)-aminomethane (Tris), magnesium chloride, NaOH, 1 M HCl and EDTA were obtained from Merck Biosciences, Darmstadt, Germany. "Complete" protease inhibitor was from Roche Diagnostics, Mannheim, Germany.

Test compounds were diluted to the appropriate concentrations in buffer 1 (25 mM Tris-HCl, pH 7.4, 5 mM MgCl₂, 2 mM DTT, 0.02 % (w/v) BSA, 0.01 % Pluronic F-68 and 3 % DMSO). The ROCK II enzyme was diluted to a concentration of 100 ng/mL in buffer 2 (25 mM Tris-HCl, pH 7.4, 5 mM MgCl₂, 2 mM DTT and 0.02 % (w/v) BSA). The peptide substrate and ATP were diluted to concentrations of 3 μ M and 120 μ M, respectively, in the buffer 2. Two μ l of the compound solution were mixed with 2 μ l of the diluted enzyme in a 384-well small volume microtiter plate (Greiner, Bio-One, Frickenhausen, Germany), and the kinase reaction was initiated by addition of 2 μ l of the solution containing peptide substrate and ATP. After 60 min incubation at 32 °C, the reaction was stopped by addition of 20 μ l of a solution containing 100 mM Hepes-NaOH, pH 7.4, 0.015 % (v/v) Brij-35, 45 mM EDTA and 0.227 % chip coating reagent 1 (Caliper Lifescience Inc, Hopkinton, MA). Phosphorylation of the substrate peptide was then detected on a Caliper 3000 instrument essentially as described by Pommereau et al (J. Biomol. Screening 9(5), 409-416, 2004). Separation conditions were as follows: Pressure -1.3 psi, upstream voltage -1562 V, downstream voltage -500 V, sample sip time 200 ms. Positive controls (buffer 1 instead of compound) and negative controls (buffer 1 instead of compound and buffer 2 instead of ROCK II) were run in parallel on each plate.

[0410] The following products/compounds were tested in said assay by using the respective form (salt or free base) obtained as in the examples described above and the following activities were measured

Example No.	pIC50
1	+++++++
2	+++++++
3	+++++++
4	+++++++
5	+++++++
6	+++++++
7	+++++++
8	+++++++
9	+++++++
10	+++++++
11	+++++++
12	+++++
13	+++++
14	+++++
15	+++++++
16	+++++++
17	+++++++
19	+++++
20	+++++++
22	+++++++
24	+++++++
25	+++++++
26	+++++++
27	+++++++

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(continued)

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Example No.	pIC50
28	+++++++
29	+++++++
31	+++++++
32	+++++++
34	+++++++
35	+++++++
36	+++++++
37	+++++++
38	+++++++
39	+++++++
40	+++++
41	+++++
42	+++++++
44	+++++++
45	+++++++
46	+++++++
51	+++++
52	+++++++
53	+++++++
54	+++++
55	+++++++
56	+++++++
57	+++++++
58	+++++++
59	+++++++
60	+++++++
61	+++++
62	+++++++
63	+++++++
64	+++++++
65	+++++
66	+++++
67	+++++
69	+++++++
70	+++++++
77	+++++++
82	+++++++
83	+++++

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(continued)

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Example No.	pIC ₅₀
84	+++++
85	+++++
86	+++++
87	++++++
88	+++++
89	+++++
90	+++++
92	+++++
94	+++++
97	+++++++
99	+++++++
100	+++++++
101	+++++
109	+++++++
110	+++++++
111	+++++++
114	+++++++
115	+++++
116	+++++++
117	+++++++
118	+++++
119	+++++
120	+++++
121	+++++++
122	+++++++
123	+++++++
124	+++++++
125	+++++
126	+++++
128	+++++
129	+++++++
130	+++++++
131	+++++

[0411] The given activity is denoted as the negative decadal logarithm of the IC₅₀ (pIC₅₀) as follows:

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+: pIC₅₀ ≤ 3.0
 ++: 3.0 ≤ pIC₅₀ < 4.0
 +++: 4.0 ≤ pIC₅₀ < 5.0

(continued)

++++: $5.0 \leq \text{pIC}_{50} < 6.0$
 +++++: $6.0 \leq \text{pIC}_{50} < 7.0$
 ++++++: $7.0 \leq \text{pIC}_{50} < 8.0$
 ++++++: $8.0 \leq \text{pIC}_{50}$

Determination of Protein Kinase A and Protein Kinase G inhibition

[0412] To measure PKA and PKG1-beta inhibition, IC_{50} values were determined according to the following protocol:

Active recombinant human PKG1-beta (full-length, with N-terminal His-tag) was purchased from Millipore GmbH, Schwalbach, Germany. Active recombinant human PKA (residues 1-351, N-terminal His-tag) was obtained from Invitrogen, Karlsruhe, Germany. The peptide substrate, Fluorescein-AKRRRLSSLRA-COOH, was obtained from JPT Peptide Technologies, Berlin, Germany. Adenosine-5'-triphosphate (ATP), bovine serum albumine (BSA), dimethylsulphoxide (DMSO), 4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid (Hepes), Brij-35, dithiothreitol (DTT) and Pluronic F-68 were purchased from Sigma-Aldrich, Munich, Germany. Tris(hydroxymethyl)-aminomethane (Tris), magnesium chloride, NaOH, 1 M HCl and EDTA were obtained from Merck Biosciences, Darmstadt, Germany. "Complete" protease inhibitor was from Roche Diagnostics, Mannheim, Germany.

Test compounds were diluted to the appropriate concentrations in buffer 1 (25 mM Tris-HCl, pH 7.4, 5 mM MgCl_2 , 2 mM DTT, 0.02 % (w/v) BSA, 0.01 % Pluronic F-68 and 3 % DMSO). PKG1-beta and PKA were diluted to concentrations of 150 ng/ml and 30 ng/ml, respectively, in buffer 2. The peptide substrate and ATP were diluted to concentrations of 3 μM and 120 μM , respectively, in the buffer 2. Two μl of the compound solution were mixed with 2 μl of the diluted enzyme in a 384-well small volume microtiter plate (Greiner, Bio-One, Frickenhausen, Germany), and the kinase reaction was initiated by addition of 2 μl of the solution containing peptide substrate and ATP. After 60 min incubation at 32 °C, the reaction was stopped by addition of 20 μl of a solution containing 100 mM Hepes-NaOH, pH 7.4, 0.015 % (v/v) Brij-35, 45 mM EDTA and 0.227 % chip coating reagent 1 (Caliper Lifescience Inc, Hopkinton, MA). Phosphorylation of the substrate peptide was then detected on a Caliper 3000 instrument essentially as described by Pommereau et al (J. Biomol. Screening 9(5), 409-416, 2004). Separation conditions were as follows: Pressure -1.3 psi, upstream voltage -1562 V, downstream voltage -500 V, sample sip time 200 ms. Positive controls (buffer 1 instead of compound) and negative controls (buffer 1 instead of compound and buffer 2 instead of kinase solution) were run in parallel on each plate. The following products/compounds were tested in said assay by using the respective form (salt or free base) obtained as in the examples described above and the following activities were measured.

Example No.	Selectivity against PKA	Selectivity against PKG
1	>1000	>1000
2	>1000	>1000
3	>1000	>300
4	>1000	>100
5	>1000	>300
6	>1000	>300
7	>1000	>300
8	>1000	>300
9	>1000	>100
10	>100	>100
11	>300	>10
12	>100	>10
13	>300	>100
14	>100	>100

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(continued)

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Example No.	Selectivity against PKA	Selectivity against PKG
15	>1000	>300
16	>300	>100
17	>300	>100
19	>100	>100
20	>100	>100
22	>300	>100
24	>1000	>300
25	>1000	>100
26	>1000	>300
27	>100	>10
28	>1000	>1000
29	>1000	>1000
31	>300	>100
32	>1000	>300
34	>300	>10
35	>1000	>100
36	>300	>300
37	>1000	>300
38	>1000	>300
39	>100	>100
41	>10	>10
42	>300	>300
44	>1000	>1000
45	>1000	>100
46	>1000	>1000
51	>100	>10
52	>1000	>300
53	>100	>100
55	>1000	>300
56	>1000	>300
57	>1000	>300
58	>1000	>100
59	>1000	>300
60	>1000	>100
61	>10	>1
62	>1000	>300
63	>1000	>300
64	>1000	>100

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(continued)

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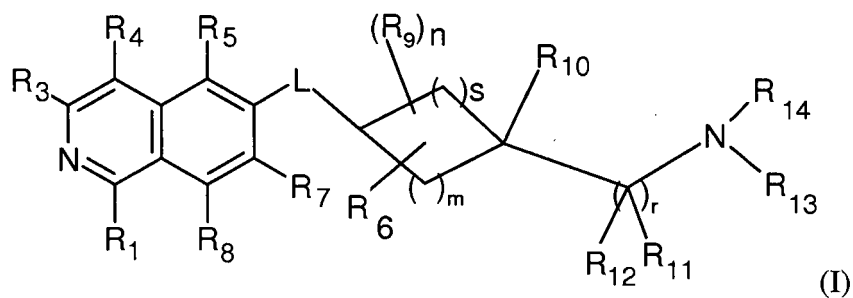
Example No.	Selectivity against PKA	Selectivity against PKG
66	>10	>10
69	>1000	>300
70	>1000	>1000
77	>1000	>300
82	>1000	>1000
83	>100	>10
84	>100	>10
85	>100	>10
86	>10	>10
87	>1000	>100
88	>10	>10
97	>1000	>300
99	>1000	>100
100	>1000	>1000
109	>300	>100
110	>300	>100
114	>1000	>1000
116	>100	>10
117	>300	>10
120	>100	>10
121	>100	>10
122	>300	>10
123	>100	>10
124	>100	>10
125	>10	>10
128	>10	>10
129	>100	>10
130	>300	>10
131	>10	>10
132	>100	>10

Claims

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1. A compound of the formula (I)

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wherein

R_1 is H, OH or NH_2 ;

R_3 is H, halogen, CN, $(\text{C}_1\text{-C}_6)\text{alkyl}$, OH, NH_2 , or NHR' ;

R_4 is H, halogen, hydroxy, CN, $(\text{C}_1\text{-C}_6)\text{alkyl}$, R' , or $(\text{C}_1\text{-C}_6)\text{alkylene-R}'$;

R_5 is H, halogen, CN, $(\text{C}_1\text{-C}_6)\text{alkyl}$, or R' ;

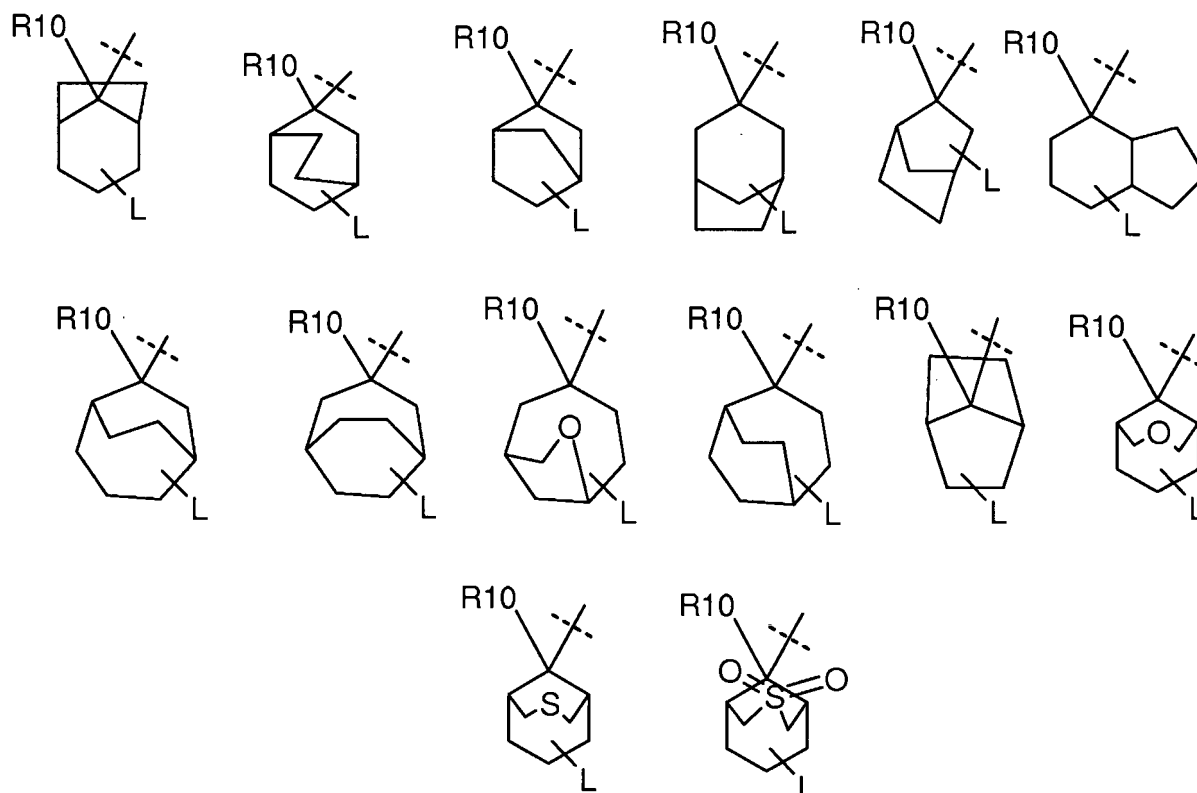
R_7 is H, halogen, CN, $(\text{C}_1\text{-C}_6)\text{alkyl}$, $\text{O-(C}_1\text{-C}_6)\text{alkyl}$, R' , or $\text{SO}_2\text{-NH}_2$;

R_8 is H, halogen or $(\text{C}_1\text{-C}_6)\text{alkyl}$;

R_9 is OH, halogen, $(\text{C}_1\text{-C}_6)\text{alkyl}$, C(O)OH , C(O)NH_2 , or O-CH_3 , wherein $(\text{C}_1\text{-C}_6)\text{alkyl}$ is unsubstituted or substituted.

R_6 is absent

or is one $(\text{C}_1\text{-C}_4)\text{alkylene}$ bond to the cycloalkyl ring, in which the $(\text{C}_1\text{-C}_4)\text{alkylene}$ forms a second bond to a different carbon atom of the cycloalkyl ring to form a bicyclic ring system of formula,



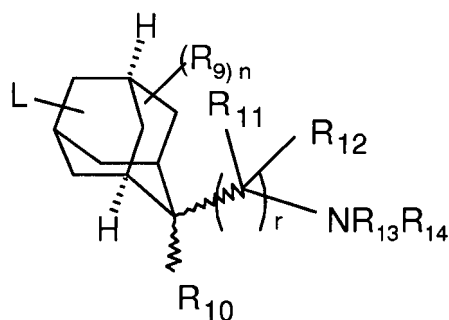
or, if m and s are 2, m is 3 and s is 1, or m is 4 and s is 0,

R_6 is $\text{CH}_2\text{-CH-(CH}_2)_2$ which is bound with one CH_2 to the cycloalkyl ring and the two other CH_2 are bound to different carbon atoms of the cycloalkyl ring;

and, if m is 3 and s is 3,

R_6 are two methylene groups bound to different carbon atoms of the cycloalkyl ring, wherein the methylene groups or the $\text{CH}_2\text{-CH-(CH}_2)_2$ group are bound to carbon atoms of the cycloalkyl ring such that they form an

adamantane system of the formula



wherein L can be bound to any secondary or tertiary carbon atom and

wherein the bicyclic ring system or adamantane system is unsubstituted or optionally substituted by R_9 ;

R_{10} is

H, phenyl, O-phenyl, or (C_5-C_6) heteroaryl,

wherein phenyl or (C_5-C_6) heteroaryl is unsubstituted or substituted;

R_{11} is

H,

(C_1-C_6) alkyl,

(C_1-C_6) alkylene- R' ,

(C_3-C_8) cycloalkyl,

(C_5-C_{10}) heteroaryl,

(C_3-C_8) heterocycloalkyl,

(C_6-C_{10}) aryl;

or R_{11} and R_{12} together with carbon atom to which they are attached form a (C_3-C_8) cycloalkyl or a (C_3-C_8) -heterocycloalkyl ring;

R_{12} is

(C_1-C_6) alkyl,

(C_3-C_8) cycloalkyl,

(C_5-C_{10}) heteroaryl,

(C_3-C_8) heterocycloalkyl, or

(C_6-C_{10}) aryl;

or R_{12} is H, provided that $r = 2$ and the other R_{12} is not H;

or R_{11} and R_{12} together with carbon atom to which they are attached form a (C_3-C_8) cycloalkyl or a (C_3-C_8) -heterocycloalkyl ring;

R_{13} and R_{14} are independently of each other

H,

R' ,

(C_1-C_6) alkyl,

(C_1-C_6) alkylene- R' ,

(C_1-C_6) alkylene-O- (C_1-C_6) alkyl,

(C_1-C_6) alkylene-O- R' ,

$C(O)(C_1-C_6)$ alkyl,

$C(O)R'$, or

$C(O)(C_1-C_6)$ alkylene- R'

$C(O)N[(C_1-C_6)alkyl]_2$,

wherein R' , (C_1-C_6) alkyl, or (C_1-C_6) alkylene are unsubstituted or substituted, or

R_{13} and R_{14} , together with the N-atom to which they are attached, form a unsubstituted or substituted (C_3-C_8) heterocycloalkyl ring.

n is 0, 1, 2, 3 or 4;

m is 1, 2, 3 or 4;

s is 0, 1, 2, or 3;

r is 1 or 2;

L is O, S, or NH;

R' is

(C₃-C₈)cycloalkyl,
 (C₅-C₁₀)heteroaryl,
 (C₃-C₈)heterocycloalkyl,
 (C₆-C₁₀)aryl;

wherein in residues R₃ to R₁₄ alkyl or alkylene is unsubstituted or optionally substituted one or more times by OH, OCH₃, C(O)OH, C(O)OCH₃, NH₂, NHCH₃, N(CH₃)₂, C(O)NH₂, C(O)NHCH₃ or C(O)N(CH₃)₂;

wherein in residues R₃ to R₁₄ cycloalkyl or heterocycloalkyl is unsubstituted or optionally substituted one or more times by (C₁-C₆)alkyl, halogen, OH, OCH₃, C(O)OH, C(O)OCH₃, NH₂, NHCH₃, N(CH₃)₂, C(O)NH₂, C(O)NHCH₃ or C(O)N(CH₃)₂;

wherein in residues R₃ to R₁₄ alkyl or alkylene is unsubstituted or optionally substituted one or more times by halogen;

wherein in residues R₃ to R₁₄ (C₆-C₁₀)aryl and (C₅-C₁₀)heteroaryl are unsubstituted or optionally substituted one or more times by a group independently selected from halogen, OH, NO₂, N₃, CN, C(O)-(C₁-C₆)alkyl, C(O)-(C₆-C₁₀)aryl, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂, (C₃-C₈)cycloalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkylene-NH(C₁-C₆)alkyl, (C₁-C₆)alkylene-N[(C₁-C₆)alkyl]₂, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, O-(C₁-C₆)alkyl, O-C(O)-(C₁-C₆)alkyl, PO₃H₂, SO₃H, SO₂-NH₂, SO₂NH(C₁-C₆)alkyl, SO₂N[(C₁-C₆)alkyl]₂, S-(C₁-C₆)alkyl; SO-(C₁-C₆)alkyl, SO₂-(C₁-C₆)alkyl SO₂-N=CH-N[(C₁-C₆)alkyl]₂, SF₅,

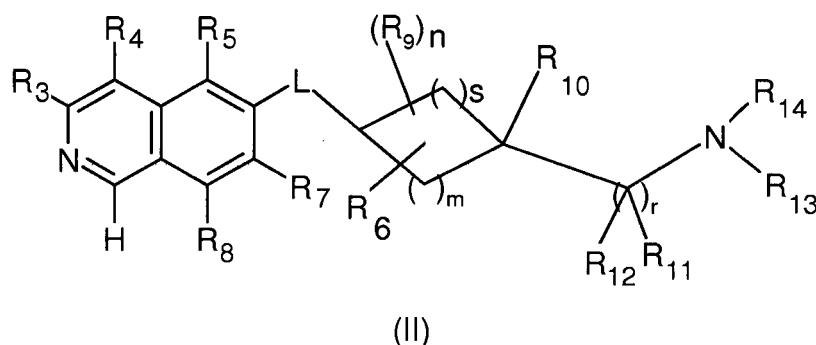
C(NH)(NH₂), NH₂, NH-(C₁-C₆)alkyl, N[(C₁-C₆)alkyl]₂, NH-C(O)-(C₁-C₆)alkyl, NH-C(O)-O-(C₁-C₆)alkyl, NH-SO₂-(C₁-C₆)alkyl, NH-SO₂-(C₆-C₁₀)aryl, NH-SO₂-(C₅-C₁₀)heteroaryl, NH-SO₂-(C₃-C₈)heterocycloalkyl, N(C₁-C₆)alkyl-C(O)-(C₁-C₆)alkyl, N(C₁-C₆)alkyl-C(O)-O-(C₁-C₆)alkyl, N(C₁-C₆)alkyl-C(O)-NH-(C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₁-C₆)alkylene-(C₆-C₁₀)aryl, O-(C₆-C₁₀)aryl, O-(C₁-C₆)alkylene-(C₆-C₁₀)aryl, (C₅-C₁₀)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₁-C₆)alkylene-(C₅-C₁₀)heteroaryl, (C₁-C₆)alkylene-(C₃-C₈)heterocycloalkyl, O-(C₁-C₆)alkylene-(C₅-C₁₀)heteroaryl, O-(C₁-C₆)alkylene-(C₃-C₈)heterocycloalkyl,

wherein said (C₆-C₁₀)aryl, (C₅-C₁₀)heteroaryl, (C₃-C₈)heterocycloalkyl or (C₃-C₈)cycloalkyl may be substituted one to three times by a group independently selected from halogen, OH, NO₂, CN, O-(C₁-C₆)alkyl, (C₁-C₆)alkyl, NH₂, NH(C₁-C₆)alkyl, N[(C₁-C₆)alkyl]₂, SO₂CH₃, COOH, C(O)-O-(C₁-C₆)alkyl, CONH₂, (C₁-C₆)alkylene-O-(C₁-C₆)alkyl, (C₁-C₆)alkylene-O-(C₆-C₁₀)aryl, or O-(C₁-C₆)alkylene-(C₆-C₁₀)aryl; or

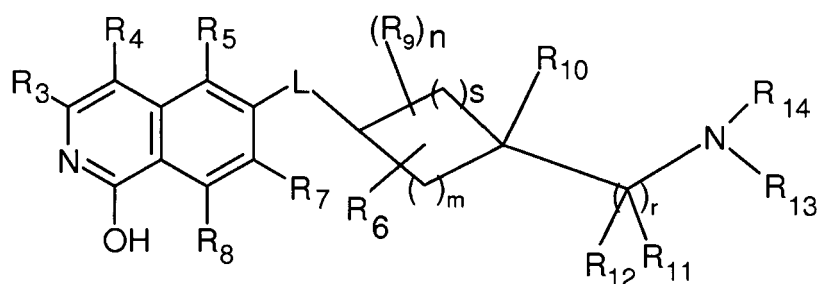
wherein (C₆-C₁₀)aryl is vicinally substituted by a O-(C₁-C₄)alkylene-O group whereby a 5-8-membered ring is formed together with the carbon atoms the oxygen atoms are attached to; and

wherein aryl substituents of (C₆-C₁₀)aryl, (C₅-C₁₀)heteroaryl, (C₃-C₈)heterocycloalkyl or (C₃-C₈)cycloalkyl groups may not be further substituted by an aryl, heteroaryl, heterocycloalkyl, or (C₃-C₈)cycloalkyl containing group; their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts.

2. A compound of formula (I) according to claim 1, wherein R₁ is H and is **characterized by** the formula (II)

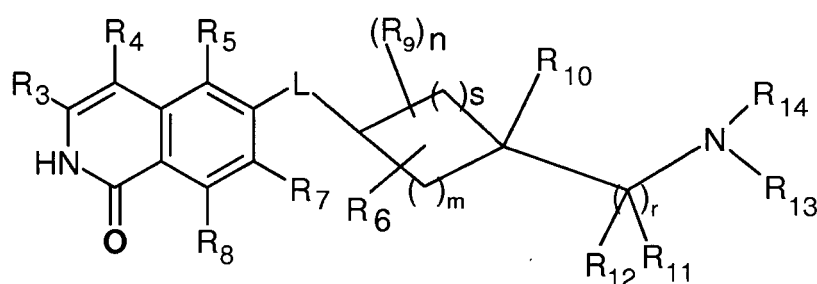


3. A compound of formula (I) according to claim 1, wherein R₁ is OH and is **characterized by** the formula (IIIa)



(IIIa)

or of the formula (IIIb)



(IIIb)

4. A compound according to claim 1, wherein R_1 is NH_2 .
5. A compound according to one of claims 1 to 4, wherein R_3 is H, halogen, $(\text{C}_1\text{-C}_6)$ alkyl, or NHR' , wherein $(\text{C}_1\text{-C}_6)$ alkyl and R' are unsubstituted or substituted.
6. A compound according to one of claims 1 to 5, wherein R_3 is H.
7. A compound according to one of claims 1 to 6, wherein R_4 is H, halogen, $(\text{C}_1\text{-C}_6)$ alkyl or $(\text{C}_1\text{-C}_2)$ alkylene-phenyl, wherein $(\text{C}_1\text{-C}_6)$ alkyl or phenyl are unsubstituted or substituted.
8. A compound according to one of claims 1 to 7, wherein R_4 is H or halogen.
9. A compound according to one of claims 1 to 8, wherein R_5 is H, halogen, $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_6\text{-C}_{10})$ aryl, $(\text{C}_3\text{-C}_8)$ cycloalkyl or $(\text{C}_5\text{-C}_{10})$ heteroaryl, wherein $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_6\text{-C}_{10})$ aryl, $(\text{C}_3\text{-C}_8)$ cycloalkyl or $(\text{C}_5\text{-C}_{10})$ heteroaryl are unsubstituted or substituted.
10. A compound according to one of claims 1 to 9, wherein R_5 is H.
11. A compound according to one of claims 1 to 10, wherein R_7 is H, halogen, $(\text{C}_1\text{-C}_6)$ alkyl, $\text{O}-(\text{C}_1\text{-C}_6)$ alkyl, or R' , wherein $(\text{C}_1\text{-C}_6)$ alkyl or R' are unsubstituted or substituted.
12. A compound according to one of claims 1 to 11, wherein R_7 is H, methyl or chloro.
13. A compound according to one of claims 1 to 12, wherein R_8 is H.
14. A compound according to one of claims 1 to 13, wherein R_9 is unsubstituted or substituted $(\text{C}_1\text{-C}_6)$ alkyl.
15. A compound according to any of claims 1 to 14, wherein R_{10} is H or phenyl optionally substituted by $(\text{C}_1\text{-C}_6)$ alkyl, F, Cl, Br, OMe or CF_3 .

16. A compound according to any of claims 1 to 15, wherein R_{10} is H.

17. A compound according to any of claims 1 to 16, wherein R_{11} is H or methyl.

18. A compound according to any of claims 1 to 17, wherein R_{12} is
 (C₁-C₆)alkyl, wherein optionally one or more hydrogen are substituted by fluoro;
 (C₃-C₈)cycloalkyl,
 (C₅-C₆)heteroaryl, or
 (C₆-C₁₀)aryl,
 wherein (C₃-C₈)cycloalkyl, (C₅-C₆)heteroaryl or (C₆-C₁₀)aryl are unsubstituted or substituted.

19. A compound according to any of claims 1 to 18, wherein R_{12} is methyl, ethyl, propyl, isopropyl, cyclopropyl, trifluoromethyl, thiazolyl or phenyl unsubstituted or substituted by (C₁-C₄)alkyl or halogen.

20. A compound according to any of claims 1 to 18, wherein R_{11} and R_{12} form a substituted or unsubstituted (C₃-C₈)cycloalkyl ring.

21. A compound according to one of claims 1 to 20, wherein R_{13} and R_{14} are independently of each other
 H,
 (C₁-C₆)alkyl,
 (C₃-C₈)cycloalkyl,
 (C₁-C₄)alkylene-(C₃-C₈)cycloalkyl,
 (C₁-C₄)alkylene-(C₅-C₁₀)heteroaryl,
 (C₁-C₄)alkylene-(C₃-C₈)heterocycloalkyl,
 (C₁-C₄)alkylene-(C₆-C₁₀)aryl,
 (C₁-C₆)alkylene-O-(C₁-C₆)alkyl,
 C(O)(C₁-C₆)alkyl, or
 R_{13} and R_{14} , together with the N-atom to which they are attached, form a (C₃-C₈) heterocycloalkyl group,
 wherein (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl, (C₁-C₄)alkylene, (C₅-C₁₀)heteroaryl, (C₃-C₈)heterocycloalkyl, or (C₆-C₁₀)aryl are unsubstituted or substituted.

22. A compound according to any of claims 1 to 21, wherein
 R_{13} is H or (C₁-C₆)alkyl; and
 R_{14} is
 H,
 (C₁-C₆)alkyl,
 (C₃-C₈)cycloalkyl,
 (C₁-C₄)alkylene-(C₃-C₈)cycloalkyl,
 (C₁-C₄)alkylene-(C₅-C₁₀)heteroaryl,
 (C₁-C₄)alkylene-(C₃-C₈)heterocycloalkyl,
 (C₁-C₄)alkylene-(C₆-C₁₀)aryl, or
 (C₁-C₄)alkylene-O-(C₁-C₆)alkyl,
 wherein (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl, (C₁-C₄)alkylene, (C₅-C₁₀)heteroaryl, (C₃-C₈)heterocycloalkyl, or (C₆-C₁₀)aryl are unsubstituted or substituted.

23. A compound according to any of claims 1 to 22, wherein
 R_{13} is H, (C₁-C₆)alkyl and
 R_{14} is H, (C₁-C₆)alkyl or (C₃-C₈)cycloalkyl,
 wherein (C₁-C₆)alkyl or (C₃-C₈)cycloalkyl are unsubstituted or substituted.

24. A compound according to any of claims 1 to 23, wherein R_{13} and R_{14} are H.

25. A compound according to one of claims 1 to 24, wherein R_6 is absent.

26. A compound according to one of claims 1 to 25, wherein m is 2 and s is 2

27. A compound according to one of claims 1 to 26, wherein m is 3 and s is 1.

28. A compound according to one of claims 1 to 27, wherein n is 0, 1, or 2.

29. A compound according to one of claims 1 to 28, wherein n is 0.

30. A compound according to one of claims 1 to 29, wherein r is 1.

31. A compound according to one of claims 1 to 30, wherein L is S,.

32. A compound according to one of claims 1 to 31, wherein L is NH.

33. A compound according to one of claims 1 to 32, wherein L is O.

34. A compound according to claim 1 selected from the group consisting of

6-[4-(1-Amino-propyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-cyclopropyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[[4-(1-aminopropyl)-4-phenylcyclohexyl]oxy]-7-chloroisoquinolin-1(2H)-one,
 6-[4-(1-Amino-butyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-butyl)-4-(4-fluoro-phenyl)-cyclo-hexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-propyl)-4-(4-bromo-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-propyl)-4-(2-bromo-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-propyl)-4-(4-trifluoromethyl-phenyl)-cyclo-hexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-propyl)-4-(2-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-propyl)-4-(2-chloro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-methyl-2H-isoquinolin-1-one,
 6-[4-(1-Amino-ethyl)-4-(4-fluoro-phenyl)-cyclo-hexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-2-methyl-propyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-3-methyl-butyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(Amino-phenyl-methyl)-4-phenyl-cyclo-hexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-1-methyl-ethyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-cyclopropyl)-4-(2-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-ethyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-1-methyl-ethyl)-4-phenyl-cyclo-hexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-(4-[amino(cyclopropyl)methyl]-4-phenyl-cyclohexyl]oxy)-7-chloroisoquinolin-1(2H)-one,
 6-[4-(1-Amino-propyl)-4-(4-isopropyl-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-propyl)-4-(3-methoxy)-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-propyl)-4-(3-bromo-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-2-methyl-propyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, or
 6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-4-bromo-7-chloro-2H-isoquinolin-1-one,
 their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts thereof.

35. A compound according to claim 1 selected from the group consisting of

cis-6-[4-(1-Amino-propyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-amino-propyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-on,
 cis-6-[4-(1-Amino-cyclopropyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[[4-(1-Amino-propyl)-4-phenylcyclohexyl]oxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Amino-propyl)-4-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-butyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Amino-butyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-butyl)-4-(4-fluoro-phenyl)-cyclo-hexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Amino-butyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amin-propyl)-4-(4-bromo-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(2-bromo-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one
 cis-6-[4-(1-Amino-propyl)-4-(4-trifluoromethyl-phenyl)-cyclo-hexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(2-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(2-chloro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-methyl-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-ethyl)-4-(4-fluoro-phenyl)-cyclo-hexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Amino-ethyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,

cis-6-[4-(1-Amino-propyl)-4-(3-bromo-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Amino-propyl)-4-(3-bromo-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3-methoxy-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Amino-propyl)-4-(3-methoxy-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(Amino-phenyl-methyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Amino-2-methyl-propyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Amino-3-methyl-butyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(Amino-phenyl-methyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Amino-1-methyl-ethyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-cyclopropyl)-4-(2-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-ethyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-1-methyl-ethyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-[amino(cyclopropyl)methyl]-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(4-isopropyl-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-2-methyl-propyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, and
 cis-6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-4-bromo-7-chloro-2H-isoquinolin-1-one,
 their stereoisomeric and/or tautomeric forms and/or pharmaceutically acceptable salts thereof.

36. A compound according to claim 1 selected from the group consisting of

trans-6-[4-((S)-Amino-phenyl-methyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-((R)-Amino-phenyl-methyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-((S)-1-Amino-propyl)-4-fluoro-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-((R)-1-Amino-propyl)-4-fluoro-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-((S)-Amino-cyclopropyl-methyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-((R)-Amino-cyclopropyl-methyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-((R)-Amino-cyclopropyl-methyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-((S)-Amino-cyclopropyl-methyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-((S)-1-Amino-ethyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-((R)-1-Amino-ethyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-((S)-Amino-(4-fluoro-phenyl)-methyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-((R)-Amino-(4-fluoro-phenyl)-methyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-((R)-1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, and
 cis-6-[4-((S)-1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, their tautomeric forms and/or
 pharmaceutically acceptable salts thereof.

37. A compound according to claim 1 selected from the group consisting of

cis-6-[4-(1-Amino-propyl)-4-pyridin-2-yl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(2,4-difluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(4-fluoro-2-methyl-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3,5-difluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3,4-difluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-o-tolyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(2-trifluoromethoxy-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(4-fluoro-3-methoxy-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3-ethoxy-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3-methoxy-4-methyl-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3,4-difluoro-phenyl)-cyclohexyloxy]-7-methyl-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3,5-difluoro-phenyl)-cyclohexyloxy]-7-fluoro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3,4-difluoro-phenyl)-cyclohexyloxy]-7-fluoro-5-methyl-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3,5-difluoro-phenyl)-cyclohexyloxy]-7-methoxy-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(2-methoxy-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(4-trifluoro-methoxy-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-1-methyl-ethyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3,5-difluoro-phenyl)-cyclohexyloxy]-4-benzyl-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3,5-difluoro-phenyl)-cyclohexyloxy]-5-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3,5-difluoro-phenyl)-cyclohexyloxy]-5,7-dimethyl-2H-isoquinolin-1-one,
 cis-6-[4-(Amino-cyclopropyl-methyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3-trifluoromethyl-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,

cis-6-[4-(1-Amino-propyl)-4-(3-trifluoromethoxy-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3-trifluoromethoxy-phenyl)-cyclohexyloxy]-7-methyl-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-(3-trifluoromethyl-phenyl)-cyclohexyloxy]-7-methyl-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-fluoro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-fluoro-5-methyl-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-4-benzyl-7-chloro-2H-isoquinolin-1-one,
 cis-4-[1-(1-Amino-propyl)-4-(7-chloro-1-oxo-1,2-dihydro-isoquinolin-6-yloxy)-cyclohexyl]-benzonitrile,
 cis-3-[1-(1-Amino-propyl)-4-(7-chloro-1-oxo-1,2-dihydro-isoquinolin-6-yloxy)-cyclohexyl]benzonitrile,
 6-[cis-4-(1-Amino-propyl)-4-(3-methanesulfonyl-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[(1S,4S,5S)-5-(1-Amino-propyl)-5-phenyl-bicyclo[2.2.1]hept-2-yloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[(1R,4R,5R)-5-(1-Amino-propyl)-5-phenyl-bicyclo[2.2.1]hept-2-yloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Benzylamino-propyl)-4-phenyl-cyclohexyloxy]-7-methyl-2H-isoquinolin-1-one,
 cis-6-[4-(1-Diethylamino-propyl)-4-phenyl-cyclohexyloxy]-7-methyl-2H-isoquinolin-1-one,
 cis-7-Methyl-6-[4-(1-propylamino-propyl)-4-(3-trifluoromethyl-phenyl)-cyclohexyloxy]-2H-isoquinolin-1-one,
 cis-6-[4-(1-Benzylamino-propyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-7-Chloro-6-[4-(1-isobutylamino-propyl)-4-phenyl-cyclohexyloxy]-2H-isoquinolin-1-one,
 cis-6-[4-(1-Butylamino-propyl)-4-phenyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-7-Chloro-6-[4-[1-(cyclopropylmethyl-amino)-propyl]-4-phenyl-cyclohexyloxy]-2H-isoquinolin-1-one,
 cis-6-[4-(2-Amino-propyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(2-Amino-butyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-2-fluoro-ethyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-3-methoxy-propyl)-4-(4-fluoro-phenyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[3-(1-Amino-propyl)-3-(4-fluoro-phenyl)-cyclobutyloxy]-7-chloro-2H-isoquinolin-1-one, and
 6-[3-(1-Amino-propyl)-3-(4-fluoro-phenyl)-cyclopentyloxy]-7-chloro-2H-isoquinolin-1-one,
 and their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts thereof.

38. A compound according to claim 1 is selected from the group consisting of

cis-1-[4-(7-Chloro-isoquinolin-6-yloxy)-1-(3,4-difluoro-phenyl)-cyclohexyl]-propylamine,
 cis-1-[4-(7-Bromo-isoquinolin-6-yloxy)-1-(3,4-difluoro-phenyl)-cyclohexyl]-propylamine,
 cis-1-[1-(3,5-Difluoro-phenyl)-4-(5,7-dimethyl-isoquinolin-6-yloxy)-cyclohexyl]-propylamine,
 cis-1-[1-(3,5-Difluoro-phenyl)-4-(7-fluoro-5-methyl-isoquinolin-6-yloxy)-cyclohexyl]-propylamine,
 cis-1-[1-(3,4-Difluoro-phenyl)-4-(7-fluoro-isoquinolin-6-yloxy)-cyclohexyl]-propylamine,
 cis-1-[4-(7-Chloro-isoquinolin-6-yloxy)-1-(3,5-difluoro-phenyl)-cyclohexyl]-propylamine,
 cis-1-[4-(5-Chloro-isoquinolin-6-yloxy)-1-(3,5-difluoro-phenyl)-cyclohexyl]-propylamine,
 cis-1-[4-(7-Chloro-isoquinolin-6-yloxy)-1-phenyl-cyclohexyl]-propylamine,
 cis-1-[4-(5,7-Dimethyl-isoquinolin-6-yloxy)-1-phenyl-cyclohexyl]-propylamine,
 cis-1-[4-(7-Fluoro-isoquinolin-6-yloxy)-1-phenyl-cyclohexyl]-propylamine,
 cis-1-[4-(5-Chloro-isoquinolin-6-yloxy)-1-phenyl-cyclohexyl]-propylamine,
 cis-1-[4-(7-Fluoro-5-methyl-isoquinolin-6-yloxy)-1-phenyl-cyclohexyl]-propylamine,
 cis-1-[4-(7-Bromo-isoquinolin-6-yloxy)-1-phenyl-cyclohexyl]-propylamine,
 cis-1-[4-(7-Methyl-isoquinolin-6-yloxy)-1-phenyl-cyclohexyl]-propylamine,
 cis-6-[4-(1-Amino-propyl)-4-phenyl-cyclohexyloxy]-7-chloro-isoquinolin-1-ylamine,
 [4-(1-Amino-propyl)-4-(4-methoxy-phenyl)-cyclohexyl]-isoquinolin-6-yl-amine, and
 1-Amino-[4-(1-amino-propyl)-4-(4-methoxy-phenyl)-cyclohexyl]-isoquinolin-6-yl-amine,
 and their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts thereof.

39. A compound according to claim 1 selected from the group consisting of

6-[4-(1-Amino-1-phenyl-ethyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[Amino-(4-methoxy-phenyl)-methyl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[Amino-(4-fluoro-phenyl)-methyl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(Amino-p-tolyl-methyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, or
 6-[4-(Amino-phenyl-methyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 and their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts thereof.

40. A compound according to claim 1 is selected from the group consisting of

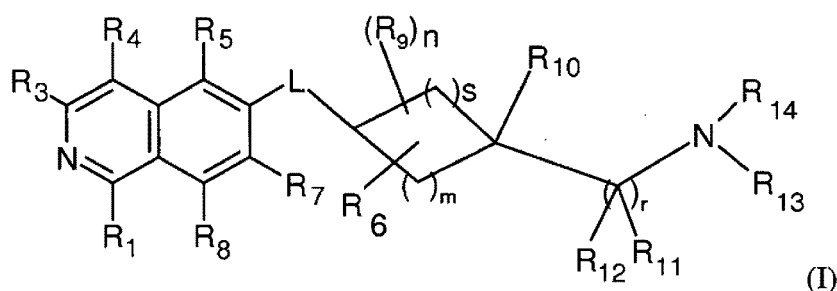
6-[4-[1-Amino-1-(4-fluoro-phenyl)-ethyl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[1-Amino-1-(4-methoxy-phenyl)-ethyl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[1-Amino-1-cyclopentyl-ethyl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,

6-[4-[1-Amino-1-ethyl-propyl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[1-Amino-1-cyclopropyl-ethyl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[1-Amino-1-n-propyl-ethyl]-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-propyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, and
 6-[4-(Amino-cyclopropyl-methyl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 and their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts thereof.

41. A compound of formula (I) and/or its pharmaceutically acceptable salt according to one of claims 1 to 41 for use as a medicament.
42. A compound of formula (I) and/or a pharmaceutically acceptable salt thereof according to one of claims 1 to 40 for use in the treatment and/or prevention of hypertension, pulmonary hypertension, ocular hypertension, retinopathy, glaucoma, peripheral circulatory disorder, peripheral arterial occlusive disease (PAOD), coronary heart disease, angina pectoris, heart hypertrophy, heart failure, ischemic diseases, ischemic organ failure (end organ damage), fibroid lung, fibroid liver, liver failure, nephropathy, renal failure, fibroid kidney, renal glomerulosclerosis, organ hypertrophy, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome, thrombotic disorders, stroke, cerebral vasospasm, cerebral ischemia, pain, neuronal degeneration, spinal cord injury, Alzheimer's disease, premature birth, erectile dysfunction, endocrine dysfunctions, arteriosclerosis, prostatic hypertrophy, diabetes and complications of diabetes, metabolic syndrome, blood vessel restenosis, atherosclerosis, inflammation, autoimmune diseases, AIDS, osteopathy, infection of digestive tracts with bacteria, sepsis or cancer development and progression.
43. A compound of formula (I) and/or a pharmaceutically acceptable salt thereof according to one of claims 1 to 40 for use in the treatment and/or prevention of hypertension, pulmonary hypertension, fibroid liver, liver failure, nephropathy, renal failure, chronic obstructive pulmonary disease (COPD), cerebral vasospasm, pain, spinal cord injury, erectile dysfunction, blood vessel restenosis, or cancer development and progression.
44. A compound of formula (I) and/or a pharmaceutically acceptable salt thereof according to one of claims 1 to 40 for use in curative approaches associated with stem cell or induced pluripotent stem cell treatment, for improvement of recognition or in the treatment or prevention of depression, epilepsy, fibroid heart, renal papillary necrosis, tubulointerstitial dysfunction, multiple sclerosis, vessel stenosis or lipid disorders.
45. A medicament comprising an effective amount of at least one compound of formula (I) and/or a pharmacologically acceptable salt thereof according to one of claims 1 to 40, pharmaceutically tolerated excipients and carriers and, where appropriate, further additives and/or other active ingredients.

Patentansprüche

1. Verbindung der Formel (I)



worin

R_1 für H, OH oder NH_2 steht;
 R_3 für H, Halogen, CN, (C_1-C_6) -Alkyl, OH, NH_2 oder NHR' steht;
 R_4 für H, Halogen, Hydroxy, CN, (C_1-C_6) -Alkyl, R' oder (C_1-C_6) -Alkyl-R' steht;
 R_5 für H, Halogen, CN, (C_1-C_6) -Alkyl oder R' steht;

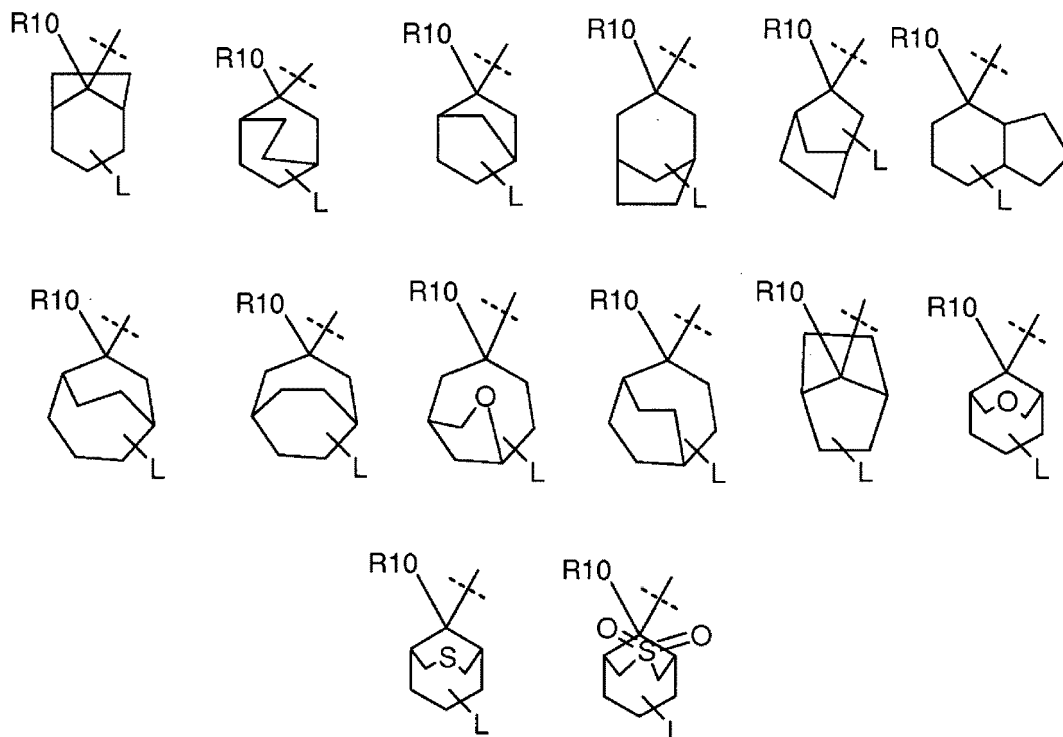
R_7 für H, Halogen, CN, (C_1-C_6) -Alkyl, $O-(C_1-C_6)$ -Alkyl, R' oder SO_2-NH_2 steht;

R_8 für H, Halogen oder (C_1-C_6) -Alkyl steht;

R_9 für OH, Halogen, (C_1-C_6) -Alkyl, $C(O)OH$, $C(O)NH_2$ oder $O-CH_3$ steht, wobei (C_1-C_6) -Alkyl unsubstituiert oder substituiert ist;

R_6 fehlt

oder für ein an den Cycloalkylring gebundenes (C_1-C_4) -Alkyl steht, wobei das (C_1-C_4) -Alkyl eine zweite Bindung mit einem anderen Kohlenstoffatom des Cycloalkylrings unter Bildung eines bicyclischen Ringsystems der Formel



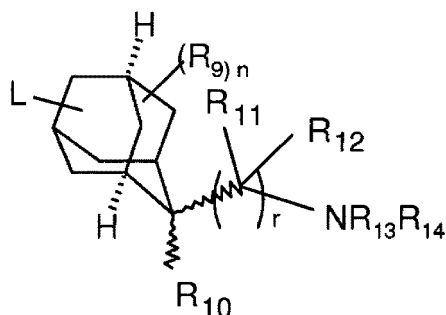
eingeht,

oder dann, wenn m und s gleich 2 sind, m gleich 3 und s gleich 1 ist oder m gleich 4 und s gleich 0 ist,

R_6 für $CH_2-CH-(CH_2)_2$ steht, das mit einem CH_2 an den Cycloalkylring gebunden ist, und die beiden anderen CH_2 an verschiedene Kohlenstoffatome des Cycloalkylrings gebunden sind;

und dann, wenn m gleich 3 und s gleich 3 ist,

R_6 für zwei an unterschiedlichen Kohlenstoffatomen des Cycloalkylrings gebundene Methylengruppen steht, wobei die Methylengruppen oder die $CH_2-CH-(CH_2)_2$ -Gruppe so an Kohlenstoffatome des Cycloalkylrings gebunden sind, dass sie ein Adamantansystem der Formel



bilden, wobei L an ein beliebiges sekundäres oder tertiäres Kohlenstoffatom gebunden sein kann und wobei das bicyclische Ringsystem oder Adamantansystem unsubstituiert oder gegebenenfalls durch R_9 substituiert ist;
 R_{10} für

H, Phenyl, 0-Phenyl oder (C₅-C₆)-Heteroaryl steht, wobei Phenyl oder (C₅-C₆)-Heteroaryl unsubstituiert oder substituiert ist;

R₁₁ für

H,

(C₁-C₆)-Alkyl,

(C₁-C₆)-Alkylen-R',

(C₃-C₈)-Cycloalkyl,

(C₅-C₁₀)-Heteroaryl,

(C₃-C₈)-Heterocycloalkyl,

(C₆-C₁₀)-Aryl

steht;

oder R₁₁ und R₁₂ zusammen mit dem Kohlenstoffatom, an das sie gebunden sind, einen (C₃-C₈)-Cycloalkyl- oder einen (C₃-C₈)-Heterocycloalkylring bilden;

R₁₂ für

(C₁-C₆)-Alkyl,

(C₃-C₈)-Cycloalkyl,

(C₅-C₁₀)-Heteroaryl,

(C₃-C₈)-Heterocycloalkyl oder

(C₆-C₁₀)-Aryl

steht;

oder R₁₂ für H steht, vorausgesetzt, dass r = 2 ist und das andere R₁₂ nicht für H steht;

oder R₁₁ und R₁₂ zusammen mit dem Kohlenstoffatom, an das sie gebunden sind, einen (C₃-C₈)-Cycloalkyl- oder einen (C₃-C₈)-Heterocycloalkylring bilden;

R₁₃ und R₁₄ unabhängig voneinander für

H,

R',

(C₁-C₆)-Alkyl,

(C₁-C₆)-Alkylen-R',

(C₁-C₆)-Alkylen-O-(C₁-C₆)-alkyl,

(C₁-C₆)-Alkylen-O-R',

C(O)-(C₁-C₆)-Alkyl,

C(O)R' oder

C(O)-(C₁-C₆)-Alkylen-R'

C(O)N[(C₁-C₆)-Alkyl]₂

stehen, wobei R', (C₁-C₆)-Alkyl oder (C₁-C₆)-Alkylen unsubstituiert oder substituiert sind, oder

R₁₃ und R₁₄ zusammen mit dem N-Atom, an das sie gebunden sind, einen unsubstituierten oder substituierten (C₃-C₈)-Heterocycloalkylring bilden;

n gleich 0, 1, 2, 3 oder 4 ist;

m gleich 1, 2, 3 oder 4 ist;

s gleich 0, 1, 2 oder 3 ist;

r gleich 1 oder 2 ist;

L für 0, S oder NH steht;

R' für

(C₃-C₈)-Cycloalkyl,

(C₅-C₁₀)-Heteroaryl,

(C₃-C₈)-Heterocycloalkyl,

(C₆-C₁₀)-Aryl

steht;

wobei in den Resten R₃ bis R₁₄ Alkyl oder Alkylen unsubstituiert oder gegebenenfalls ein- oder mehrfach durch OH, OCH₃, C(O)OH, C(O)OCH₃, NH₂, NHCH₃, N(CH₃)₂, C(O)NH₂, C(O)NHCH₃ oder C(O)N(CH₃)₂ substituiert ist;

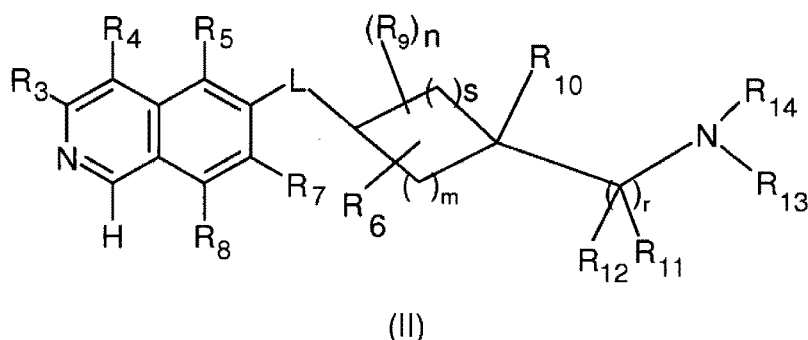
wobei in den Resten R₃ bis R₁₄ Cycloalkyl oder Heterocycloalkyl unsubstituiert oder gegebenenfalls ein- oder mehrfach durch (C₁-C₆)-Alkyl, Halogen, OH, OCH₃, C(O)OH, C(O)OCH₃, NH₂, NHCH₃, N(CH₃)₂, C(O)NH₂, C(O)NHCH₃ oder C(O)N(CH₃)₂ substituiert ist;

wobei in den Resten R₃ bis R₁₄ Alkyl oder Alkylen unsubstituiert oder gegebenenfalls ein- oder mehrfach durch Halogen substituiert ist;

wobei in den Resten R₃ bis R₁₄ (C₆-C₁₀)-Aryl und (C₅-C₁₀)-Heteroaryl unsubstituiert oder gegebenenfalls ein- oder mehrfach durch eine unabhängig aus Halogen, OH, NO₂, N₃, CN, C(O)-(C₁-C₆)-Alkyl, C(O)-(C₆-C₁₀)-Aryl, C(O)OH,

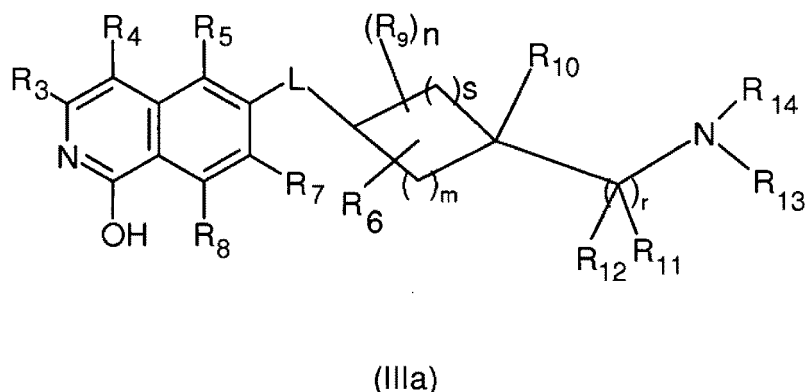
$C(O)O(C_1-C_6)\text{-Alkyl}$, $C(O)NH_2$, $C(O)NH(C_1-C_6)\text{-Alkyl}$, $C(O)N(C_1-C_6)\text{-Alkyl}]_2$, $(C_3-C_8)\text{-Cycloalkyl}$, $(C_1-C_6)\text{-Alkyl}$,
 $(C_1-C_6)\text{-Alkylen-NH}(C_1-C_6)\text{-alkyl}$, $(C_1-C_6)\text{-Alkylen-N}[(C_1-C_6)\text{-alkyl}]_2$, $(C_2-C_6)\text{-Alkenyl}$, $(C_2-C_6)\text{-Alkinyl}$,
 $O(C_1-C_6)\text{-Alkyl}$, $O-C(O)-(C_1-C_6)\text{-Alkyl}$, PO_3H_2 , SO_3H , SO_2NH_2 , $SO_2NH(C_1-C_6)\text{-Alkyl}$, $SO_2N[(C_1-C_6)\text{-Alkyl}]_2$,
 $S(C_1-C_6)\text{-Alkyl}$, $SO(C_1-C_6)\text{-Alkyl}$, $SO_2(C_1-C_6)\text{-Alkyl}$, $SO_2N=CH-N[(C_1-C_6)\text{-Alkyl}]_2$, SF_5 , $C(NH)(NH_2)$, NH_2 ,
 $NH(C_1-C_6)\text{-Alkyl}$, $N[(C_1-C_6)\text{-Alkyl}]_2$, $NH-C(O)-(C_1-C_6)\text{-Alkyl}$, $NH-C(O)O(C_1-C_6)\text{-Alkyl}$, $NH-SO_2(C_1-C_6)\text{-Alkyl}$, $NH-$
 $SO_2-(C_6-C_{10})\text{-Aryl}$, $NH-SO_2-(C_5-C_{10})\text{-Heteroaryl}$, $NH-SO_2-(C_3-C_3)\text{-Heterocycloalkyl}$, $N(C_1-C_6)\text{-Alkyl-}$
 $C(O)-(C_1-C_6)\text{-alkyl}$, $N(C_1-C_6)\text{-Alkyl-C(O)O}(C_1-C_6)\text{-alkyl}$, $N(C_1-C_6)\text{-Alkyl-C(O)-NH}(C_1-C_6)\text{-alkyl}]$, $(C_6-C_{10})\text{-Aryl}$,
 $(C_1-C_6)\text{-Alkylen-(C}_6\text{-C}_{10})\text{-aryl}$, $O-(C_6-C_{10})\text{-Aryl}$, $O-(C_1-C_6)\text{-Alkylen-(C}_6\text{-C}_{10})\text{-aryl}$, $(C_5-C_{10})\text{-Heteroaryl}$, $(C_3-C_8)\text{-He-}$
 $terocycloalkyl$, $(C_1-C_6)\text{-Alkylen-(C}_5\text{-C}_{10})\text{-heteroaryl}$, $(C_1-C_6)\text{-Alkylen-(C}_3\text{-C}_8)\text{-heterocycloalkyl}$, $O-(C_1-C_6)\text{-Alky-}$
 $len-(C}_5\text{-C}_{10})\text{-heteroaryl}$ und $O-(C_1-C_6)\text{-Alkylen-(C}_3\text{-C}_8)\text{-heterocycloalkyl}$ ausgewählte Gruppe substituiert sind, wo-
bei das $(C_6-C_{10})\text{-Aryl}$ oder $(C_5-C_{10})\text{-Heteroaryl}$ oder $(C_3-C_8)\text{-Heterocycloalkyl}$ oder $(C_3-C_8)\text{-Cycloalkyl}$ ein- bis drei-
fach durch eine unabhängig aus Halogen, OH, NO_2 , CN, $O-(C_1-C_6)\text{-Alkyl}$, $(C_1-C_6)\text{-Alkyl}$, NH_2 , $NH(C_1-C_6)\text{-Alkyl}$,
 $N[(C_1-C_6)\text{-Alkyl}]_2$, SO_2CH_3 , $C(O)OH$, $C(O)O(C_1-C_6)\text{-Alkyl}$, $C(O)NH_2$, $(C_1-C_6)\text{-Alkylen-O}(C_1-C_6)\text{-alkyl}$, $(C_1-C_6)\text{-Alky-}$
 $len-O-(C}_6\text{-C}_{10})\text{-aryl}$ und $O-(C_1-C_6)\text{-Alkylen-(C}_6\text{-C}_{10})\text{-aryl}$ ausgewählte Gruppe substituiert sein kann;
oder wobei $(C_6-C_{10})\text{-Aryl}$ vicinal durch eine $O-(C_1-C_4)\text{-Alkylen-O-Gruppe}$ substituiert ist, wodurch zusammen mit
den Kohlenstoffatomen, an die die Sauerstoffatome gebunden sind, ein 5-8-gliedriger Ring gebildet wird; und
wobei Arylsubstituenten von $(C_6-C_{10})\text{-Aryl-}$, $(C_5-C_{10})\text{-Heteroaryl-}$, $(C_3-C_8)\text{-Heterocycloalkyl-}$ oder $(C_3-C_8)\text{-Cycloal-}$
 $kylgruppen$ nicht weiter durch eine aryl-, heteroaryl-, heterocycloalkyl- oder $(C_3-C_8)\text{-cycloalkylhaltige}$ Gruppe sub-
stituiert sein können;
ihre stereoisomeren und/oder tautomeren Formen und/oder ihre pharmazeutisch unbedenklichen Salze.

2. Verbindung der Formel (I) nach Anspruch 1, wobei R_1 für H steht und durch die Formel (II)

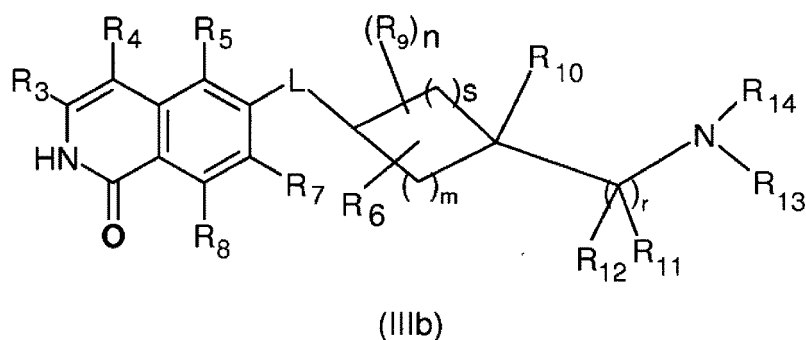


gekennzeichnet ist.

3. Verbindung der Formel (I) nach Anspruch 1, wobei R_1 für OH steht und durch die Formel (IIIa)



oder die Formel (IIIb)



gekennzeichnet ist.

4. Verbindung nach Anspruch 1, wobei R_1 für NH_2 steht.
5. Verbindung nach einem der Ansprüche 1 bis 4, wobei R_3 für H, Halogen, (C_1-C_6) -Alkyl oder NHR' steht, wobei (C_1-C_6) -Alkyl und R' unsubstituiert oder substituiert sind.
6. Verbindung nach einem der Ansprüche 1 bis 5, wobei R_3 für H steht.
7. Verbindung nach einem der Ansprüche 1 bis 6, wobei R_4 für H, Halogen, (C_1-C_6) -Alkyl oder (C_1-C_2) -Alkenylphenyl steht, wobei (C_1-C_6) -Alkyl oder Phenyl unsubstituiert oder substituiert sind.
8. Verbindung nach einem der Ansprüche 1 bis 7, wobei R_4 für H oder Halogen steht.
9. Verbindung nach einem der Ansprüche 1 bis 8, wobei R_5 für H, Halogen, (C_1-C_6) -Alkyl, (C_6-C_{10}) -Aryl, (C_3-C_8) -Cycloalkyl oder (C_5-C_{10}) -Heteroaryl steht, wobei (C_1-C_6) -Alkyl, (C_6-C_{10}) -Aryl, (C_3-C_8) -Cycloalkyl oder (C_5-C_{10}) -Heteroaryl unsubstituiert oder substituiert sind.
10. Verbindung nach einem der Ansprüche 1 bis 9, wobei R_5 für H steht.
11. Verbindung nach einem der Ansprüche 1 bis 10, wobei R_7 für H, Halogen, (C_1-C_6) -Alkyl, $O-(C_1-C_6)$ -Alkyl oder R' steht, wobei (C_1-C_6) -Alkyl oder R' unsubstituiert oder substituiert sind.
12. Verbindung nach einem der Ansprüche 1 bis 11, wobei R_7 für H, Methyl oder Chlor steht.
13. Verbindung nach einem der Ansprüche 1 bis 12, wobei R_8 für H steht.
14. Verbindung nach einem der Ansprüche 1 bis 13, wobei R_9 für unsubstituiertes oder substituiertes (C_1-C_6) -Alkyl steht.
15. Verbindung nach einem der Ansprüche 1 bis 14, wobei R_{10} für H oder Phenyl, das gegebenenfalls durch (C_1-C_6) -Alkyl, F, Cl, Br, OMe oder CF_3 substituiert ist, steht.
16. Verbindung nach einem der Ansprüche 1 bis 15, wobei R_{10} für H steht.
17. Verbindung nach einem der Ansprüche 1 bis 16, wobei R_{11} für H oder Methyl steht.
18. Verbindung nach einem der Ansprüche 1 bis 17, wobei R_{12} für (C_1-C_6) -Alkyl, wobei gegebenenfalls ein oder mehrere Wasserstoffatome durch Fluor substituiert sind; (C_3-C_8) -Cycloalkyl, (C_5-C_6) -Heteroaryl oder (C_6-C_{10}) -Aryl steht, wobei (C_3-C_8) -Cycloalkyl, (C_5-C_6) -Heteroaryl oder (C_6-C_{10}) -Aryl unsubstituiert oder substituiert sind.
19. Verbindung nach einem der Ansprüche 1 bis 18, wobei R_{12} für Methyl, Ethyl, Propyl, Isopropyl, Cyclopropyl, Trifluormethyl, Thiazolyl oder Phenyl, das unsubstituiert oder durch (C_1-C_4) -Alkyl oder Halogen substituiert ist, steht.

20. Verbindung nach einem der Ansprüche 1 bis 18, wobei R_{11} und R_{12} einen substituierten oder unsubstituierten (C₃-C₈)-Cycloalkylring bilden.

21. Verbindung nach einem der Ansprüche 1 bis 20, wobei R_{13} und R_{14} unabhängig voneinander für

H,
(C₁-C₆)-Alkyl,
(C₃-C₈)-Cycloalkyl,
(C₁-C₄)-Alkyl-(C₃-C₈)-cycloalkyl,
(C₁-C₄-Alkyl-(C₅-C₁₀)-heteroaryl,
(C₁-C₄-Alkyl-(C₃-C₈)-heterocycloalkyl,
(C₁-C₄)-Alkyl-(C₆-C₁₀)-aryl,
(C₁-C₆)-Alkyl-O-(C₁-C₆)-alkyl oder
C(O)-(C₁-C₆)-Alkyl
stehen oder

R_{13} und R_{14} zusammen mit dem N-Atom, an das sie gebunden sind, eine (C₃-C₈)-Heterocycloalkylgruppe bilden, wobei (C₁-C₆)-Alkyl, (C₃-C₈)-Cycloalkyl, (C₁-C₄)-Alkyl, (C₅-C₁₀)-Heteroaryl, (C₃-C₈)-Heterocycloalkyl oder (C₆-C₁₀)-Aryl unsubstituiert oder substituiert sind.

22. Verbindung nach einem der Ansprüche 1 bis 21, wobei

R_{13} für H oder (C₁-C₆)-Alkyl steht; und
 R_{14} für

H,
(C₁-C₆)-Alkyl,
(C₃-C₈)-Cycloalkyl,
(C₁-C₄)-Alkyl-(C₃-C₈)-cycloalkyl,
(C₁-C₄)-Alkyl-(C₅-C₁₀)-heteroaryl,
(C₁-C₄)-Alkyl-(C₃-C₈)-heterocycloalkyl,
(C₁-C₄)-Alkyl-(C₆-C₁₀)-aryl, oder
(C₁-C₄)-Alkyl-O-(C₁-C₆)-alkyl

steht,
wobei (C₁-C₆)-Alkyl, (C₃-C₈)-Cycloalkyl, (C₁-C₄)-Alkyl, (C₅-C₁₀)-Heteroaryl, (C₃-C₈)-Heterocycloalkyl oder (C₆-C₁₀)-Aryl unsubstituiert oder substituiert sind.

23. Verbindung nach einem der Ansprüche 1 bis 22, wobei

R_{13} für H oder (C₁-C₆)-Alkyl steht und
 R_{14} für H, (C₁-C₆)-Alkyl oder (C₃-C₈)-Cycloalkyl steht,
wobei (C₁-C₆)-Alkyl oder (C₃-C₈)-Cycloalkyl unsubstituiert oder substituiert sind.

24. Verbindung nach einem der Ansprüche 1 bis 23, wobei R_{13} und R_{14} für H stehen.

25. Verbindung nach einem der Ansprüche 1 bis 24, wobei R_6 fehlt.

26. Verbindung nach einem der Ansprüche 1 bis 25, wobei m gleich 2 ist und s gleich 2 ist.

27. Verbindung nach einem der Ansprüche 1 bis 26, wobei m gleich 3 ist und s gleich 1 ist.

28. Verbindung nach einem der Ansprüche 1 bis 27, wobei n gleich 0, 1 oder 2 ist.

29. Verbindung nach einem der Ansprüche 1 bis 28, wobei n gleich 0 ist.

30. Verbindung nach einem der Ansprüche 1 bis 29, wobei r gleich 1 ist.

31. Verbindung nach einem der Ansprüche 1 bis 30, wobei L für S steht.

32. Verbindung nach einem der Ansprüche 1 bis 31, wobei L für NH steht.

33. Verbindung nach einem der Ansprüche 1 bis 32, wobei L für O steht.

34. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe bestehend aus

6-[4-(1-Aminopropyl)-4-(4-fluorphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-(1-Aminocyclopropyl)-4-phenyl-cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-(1-Aminopropyl)-4-phenylcyclohexyl]oxy]-7-chlorisochinolin-1(2H)-on,
 6-[4-(1-Aminobutyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-(1-Aminobutyl)-4-(4-fluorphenyl)cyclohexyl-oxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-(1-Aminopropyl)-4-(4-bromphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-(1-Aminopropyl)-4-(2-bromphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-(1-Aminopropyl)-4-(4-trifluormethylphenyl)-cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-(1-Aminopropyl)-4-(2-fluorphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-(1-Aminopropyl)-4-(2-chlorphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-(1-Aminopropyl)-4-phenylcyclohexyloxy]-7-methyl-2H-isochinolin-1-on,
 6-[4-(1-Aminoethyl)-4-(4-fluorphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-(1-Amino-2-methylpropyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-(1-Amino-3-methylbutyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-(Aminophenylmethyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-(1-Amino-1-methylethyl)-4-(4-fluorphenyl)-cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-(1-Aminocyclopropyl)-4-(2-fluorphenyl)-cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-(1-Aminoethyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-(1-Amino-1-methylethyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-[Amino(cyclopropyl)methyl]-4-phenylcyclohexyl]oxy]-7-chlorisochinolin-1(2H)-on
 6-[4-(1-Aminopropyl)-4-(4-isopropylphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-(1-Aminopropyl)-4-(3-methoxy)phenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-(1-Aminopropyl)-4-(3-bromphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-(1-Amino-2-methylpropyl)-4-(4-fluorphenyl)-cyclohexyloxy]-7-chlor-2H-isochinolin-1-on oder 6-[4-(1-Aminopropyl)-4-phenylcyclohexyloxy]-4-brom-7-chlor-2H-isochinolin-1-on,
 ihre stereoisomeren und/oder tautomeren Formen und/oder ihre pharmazeutisch unbedenklichen Salze.

35. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe bestehend aus

cis-6-[4-(1-Aminopropyl)-4-(4-fluorphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 trans-6-[4-(1-Aminopropyl)-4-(4-fluorphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,,
 cis-6-[4-(1-Aminocyclopropyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-phenylcyclohexyl]oxy]-7-chlor-2H-isochinolin-1-on,
 trans-6-[4-(1-Aminopropyl)-4-phenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminobutyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 trans-6-[4-(1-Aminobutyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminobutyl)-4-(4-fluorphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 trans-6-[4-(1-Aminobutyl)-4-(4-fluorphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(4-bromphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(2-bromphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(4-trifluormethylphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(2-fluorphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(2-chlorphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-phenylcyclohexyloxy]-7-methyl-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminoethyl)-4-(4-fluorphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 trans-6-[4-(1-Aminoethyl)-4-(4-fluorphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(3-bromphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 trans-6-[4-(1-Aminopropyl)-4-(3-bromphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(3-methoxy)phenyl)-cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 trans-6-[4-(1-Aminopropyl)-4-(3-methoxyphenyl)-cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 trans-6-[4-(Aminophenylmethyl)-4-(4-fluorphenyl)-cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 trans-6-[4-(1-Amino-2-methylpropyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 trans-6-[4-(1-Amino-3-methylbutyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 trans-6-[4-(Aminophenylmethyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 trans-6-[4-(1-Amino-1-methylethyl)-4-(4-fluorphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminocyclopropyl)-4-(2-fluorphenyl)-cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminoethyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Amino-1-methylethyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,

cis-6-[4-[Amino(cyclopropyl)methyl]-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(4-isopropylphenyl)-cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Amino-2-methylpropyl)-4-(4-fluorphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on und
 cis-6-[4-(1-Aminopropyl)-4-phenylcyclohexyloxy]-4-brom-7-chlor-2H-isochinolin-1-on,
 ihre stereoisomeren und/oder tautomeren Formen und/oder ihre pharmazeutisch unbedenklichen Salze.

36. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe bestehend aus

trans-6-[4-((S)-Aminophenylmethyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 trans-6-[4-((R)-Aminophenylmethyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-((S)-1-Aminopropyl)-4-fluorphenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-((R)-1-Aminopropyl)-4-fluorphenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-((S)-Aminocyclopropylmethyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-((R)-Aminocyclopropylmethyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-((R)-Aminocyclopropylmethyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-((S)-Aminocyclopropylmethyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-((S)-1-Aminoethyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-((R)-1-Aminoethyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-((S)-Amino-(4-fluorphenyl)methyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-((R)-Amino-(4-fluorphenyl)methyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-((R)-1-Aminopropyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on und
 cis-6-[4-((S)-1-Aminopropyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 ihre tautomeren Formen und/oder ihre pharmazeutisch unbedenklichen Salze.

37. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe bestehend aus

cis-6-[4-(1-Aminopropyl)-4-pyridin-2-ylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(2,4-difluorphenyl)-cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(4-fluor-2-methylphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(3,5-difluorphenyl)-cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(3,4-difluorphenyl)-cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-o-tolylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(2-trifluormethoxyphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(4-fluor-3-methoxyphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(3-ethoxyphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(3-methoxy-4-methylphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(3,4-difluorphenyl)-cyclohexyloxy]-7-methyl-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(3,5-difluorphenyl)-cyclohexyloxy]-7-fluor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(3,4-difluorphenyl)-cyclohexyloxy]-7-fluor-5-methyl-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(3,5-difluorphenyl)-cyclohexyloxy]-7-methoxy-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(2-methoxyphenyl)-cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(4-trifluormethoxyphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Amino-1-methylethyl)-4-(4-fluorphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(3,5-difluorphenyl)-cyclohexyloxy]-4-benzyl-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(3,5-difluorphenyl)-cyclohexyloxy]-5-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(3,5-difluorphenyl)-cyclohexyloxy]-5,7-dimethyl-2H-isochinolin-1-on,
 cis-6-[4-(Aminocyclopropylmethyl)-4-(4-fluorphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(3-trifluormethylphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(3-trifluormethoxyphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(3-trifluormethoxyphenyl)cyclohexyloxy]-7-methyl-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-(3-trifluormethylphenyl)cyclohexyloxy]-7-methyl-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-phenylcyclohexyloxy]-7-fluor-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-phenylcyclohexyloxy]-7-fluor-5-methyl-2H-isochinolin-1-on,
 cis-6-[4-(1-Aminopropyl)-4-phenylcyclohexyloxy]-4-benzyl-7-chlor-2H-isochinolin-1-on,
 cis-4-[1-(1-Aminopropyl)-4-(7-chlor-1-oxo-1,2-dihydroisochinolin-6-yloxy)cyclohexyl]benzonitril,
 cis-3-[1-(1-Aminopropyl)-4-(7-chlor-1-oxo-1,2-dihydroisochinolin-6-yloxy)cyclohexyl]benzonitril,
 6-[cis-4-(1-Aminopropyl)-4-(3-methansulfonylphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[(1S,4S,5S)-5-(1-Aminopropyl)-5-phenylbicyclo[2.2.1]hept-2-yloxy]-7-chlor-2H-isochinolin-1-on,
 6-[(1R,4R,5R)-5-(1-Aminopropyl)-5-phenylbicyclo[2.2.1]hept-2-yloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Benzylaminopropyl)-4-phenylcyclohexyloxy]-7-methyl-2H-isochinolin-1-on,

cis-6-[4-(1-Diethylaminopropyl)-4-phenylcyclohexyloxy]-7-methyl-2H-isochinolin-1-on,
 cis-7-Methyl-6-[4-(1-propylaminopropyl)-4-(3-trifluormethylphenyl)cyclohexyloxy]-2H-isochinolin-1-on,
 cis-6-[4-(1-Benzylaminopropyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-7-Chlor-6-[4-(1-isobutylaminopropyl)-4-phenylcyclohexyloxy]-2H-isochinolin-1-on,
 cis-6-[4-(1-Butylaminopropyl)-4-phenylcyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-7-Chlor-6-[4-(1-(cyclopropylmethylamino)-propyl)-4-phenylcyclohexyloxy]-2H-isochinolin-1-on,
 cis-6-[4-(2-Aminopropyl)-4-(4-fluorphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(2-Aminobutyl)-4-(4-fluorphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Amino-2-fluorethyl)-4-(4-fluorphenyl)-cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 cis-6-[4-(1-Amino-3-methoxypropyl)-4-(4-fluorphenyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[3-(1-Aminopropyl)-3-(4-fluorphenyl)cyclobutyloxy]-7-chlor-2H-isochinolin-1-on und
 6-[3-(1-Aminopropyl)-3-(4-fluorphenyl)cyclopentyloxy]-7-chlor-2H-isochinolin-1-on,
 und ihre stereoisomeren und/oder tautomeren Formen und/oder ihre pharmazeutisch unbedenklichen Salze.

38. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe bestehend aus
 cis-1-[4-(7-Chlorisochinolin-6-yloxy)-1-(3,4-difluorphenyl)cyclohexyl]propylamin,
 cis-1-[4-(7-Bromisochinolin-6-yloxy)-1-(3,4-difluorphenyl)cyclohexyl]propylamin,
 cis-1-[1-(3,5-Difluorphenyl)-4-(5,7-dimethylisochinolin-6-yloxy)cyclohexyl]propylamin,
 cis-1-[1-(3,5-Difluorphenyl)-4-(7-fluor-5-methylisochinolin-6-yloxy)cyclohexyl]propylamin,
 cis-1-[1-(3,4-Difluorphenyl)-4-(7-fluorisochinolin-6-yloxy)cyclohexyl]propylamin,
 cis-1-[4-(7-Chlorisochinolin-6-yloxy)-1-(3,5-difluorphenyl)cyclohexyl]propylamin,
 cis-1-[4-(5-Chlorisochinolin-6-yloxy)-1-(3,5-difluorphenyl)cyclohexyl]propylamin,
 cis-1-[4-(7-Chlorisochinolin-6-yloxy)-1-phenylcyclohexyl]propylamin,
 cis-1-[4-(5,7-Dimethylisochinolin-6-yloxy)-1-phenylcyclohexyl]propylamin,
 cis-1-[4-(7-Fluorisochinolin-6-yloxy)-1-phenylcyclohexyl]propylamin,
 cis-1-[4-(5-Chlorisochinolin-6-yloxy)-1-phenylcyclohexyl]propylamin,
 cis-1-[4-(7-Fluor-5-methylisochinolin-6-yloxy)-1-phenylcyclohexyl]propylamin,
 cis-1-[4-(7-Bromisochinolin-6-yloxy)-1-phenylcyclohexyl]propylamin,
 cis-1-[4-(7-Methylisochinolin-6-yloxy)-1-phenylcyclohexyl]propylamin,
 cis-6-[4-(1-Aminopropyl)-4-phenylcyclohexyloxy]-7-chlorisochinolin-1-ylamin,
 [4-(1-Aminopropyl)-4-(4-methoxyphenyl)cyclohexyl]-isochinolin-6-ylamin und
 1-Amino-[4-(1-Aminopropyl)-4-(4-methoxyphenyl)-cyclohexyl]isochinolin-6-ylamin,
 und ihre stereoisomeren und/oder tautomeren Formen und/oder ihre pharmazeutisch unbedenklichen Salze.

39. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe bestehend aus
 6-[4-(1-Amino-1-phenylethyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-[Amino-(4-methoxyphenyl)methyl]cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-[Amino-(4-fluorphenyl)methyl]cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-(Amino-p-tolylmethyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on oder
 6-[4-(Aminophenylmethyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 und ihre stereoisomeren und/oder tautomeren Formen und/oder ihre pharmazeutisch unbedenklichen Salze.

40. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe bestehend aus
 6-[4-[1-Amino-1-(4-fluorphenyl)ethyl]cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-[1-Amino-1-(4-methoxyphenyl)ethyl]cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-[1-Amino-1-cyclopentylethyl]cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-[1-Amino-1-ethylpropyl]cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-[1-Amino-1-cyclopropylethyl]cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-[1-Amino-1-n-propylethyl]cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 6-[4-(1-Aminopropyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on und
 6-[4-(Aminocyclopropylmethyl)cyclohexyloxy]-7-chlor-2H-isochinolin-1-on,
 und ihre stereoisomeren und/oder tautomeren Formen und/oder ihre pharmazeutisch unbedenklichen Salze.

41. Verbindung der Formel (I) und/oder ihr pharmazeutisch unbedenkliches Salz nach einem der Ansprüche 1 bis 40 zur Verwendung als Arzneimittel.

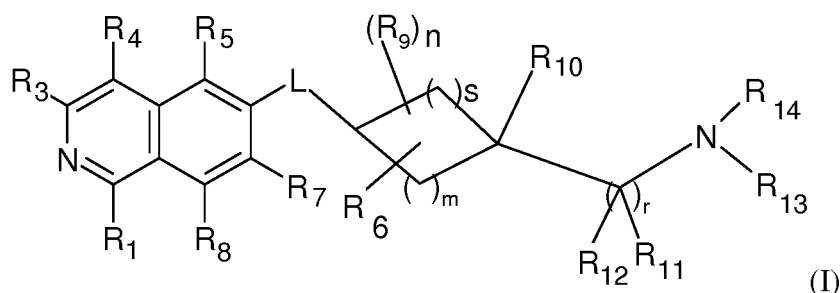
42. Verbindung der Formel (I) und/oder ihr pharmazeutisch unbedenkliches Salz nach einem der Ansprüche 1 bis 40 zur Verwendung bei der Behandlung und/oder Prävention von Hypertonie, pulmonaler Hypertonie, okulärer Hyper-

tonie, Retinopathie, Glaukom, peripherer Durchblutungsstörung, peripherer arterieller Verschlusskrankheit (PAVK), koronarer Herzkrankheit, Angina pectoris, Herzhypertrophie, Herzversagen, ischämischen Erkrankungen, ischämischen Organversagen (Endorganschaden), Lungenfibrose, Leberfibrose, Leberversagen, Nephropathie, Nierenversagen, Nierenfibrose, Nierenglomerulosklerose, Organhypertrophie, Asthma, chronisch obstruktiver Lungenerkrankung (COPD), Schocklunge, thrombotischen Störungen, Schlaganfall, zerebralen Vasospasmen, zerebraler Ischämie, Schmerzen, neuronaler Degeneration, Rückenmarkverletzung, Alzheimer-Krankheit, Frühgeburt, erektiler Dysfunktion, endokrinen Dysfunktionen, Arteriosklerose, Prostatahypertrophie, Diabetes und Komplikationen von Diabetes, metabolischem Syndrom, Blutgefäßrestenose, Atherosklerose, Entzündungen, Autoimmunerkrankungen, AIDS, Osteopathie, Infektion des Verdauungstrakts mit Bakterien, Sepsis oder Krebsentwicklung und -progression.

43. Verbindung der Formel (I) und/oder ihr pharmazeutisch unbedenkliches Salz nach einem der Ansprüche 1 bis 40 zur Verwendung bei der Behandlung und/oder Prävention von Hypertonie, pulmonaler Hypertonie, Leberfibrose, Leberversagen, Nephropathie, Nierenversagen, chronisch obstruktiver Lungenerkrankung (COPD), zerebralen Vasospasmen, Schmerzen, Rückenmarkverletzung, erektiler Dysfunktion, Blutgefäßrestenose oder Krebsentwicklung und -progression.
44. Verbindung der Formel (I) und/oder pharmazeutisch unbedenkliches Salz davon nach einem der Ansprüche 1 bis 40 zur Verwendung bei Heilungsansätzen im Zusammenhang mit der Behandlung mit Stammzellen oder induzierten pluripotenten Stammzellen, zur Verbesserung der Erkennung oder zur Behandlung oder Prävention von Depression, Epilepsie, Herzfibrose, Nierenpapillen-Nekrose, tubulointerstitieller Dysfunktion, multipler Sklerose, Gefäßrestenose oder Lipidstörungen.
45. Arzneimittel, umfassend eine wirksame Menge mindestens einer Verbindung der Formel (I) und/oder eines pharmakologisch unbedenklichen Salzes davon nach einem der Ansprüche 1 bis 40, physiologisch verträgliche Hilfsstoffe und Träger und gegebenenfalls weitere Additive und/oder andere Wirkstoffe.

Revendications

1. Composé de formule (I)



dans laquelle

R_1 représente H, OH ou NH_2 ;

R_3 représente H, un halogène, CN, alkyle (en C_1-C_6), OH, NH_2 ou NHR' ;

R_4 représente H, un halogène, hydroxy, CN, alkyle (en C_1-C_6), R' ou alkylène(en C_1-C_6)- R' ;

R_5 représente H, un halogène, CN, alkyle (en C_1-C_6) ou R' ;

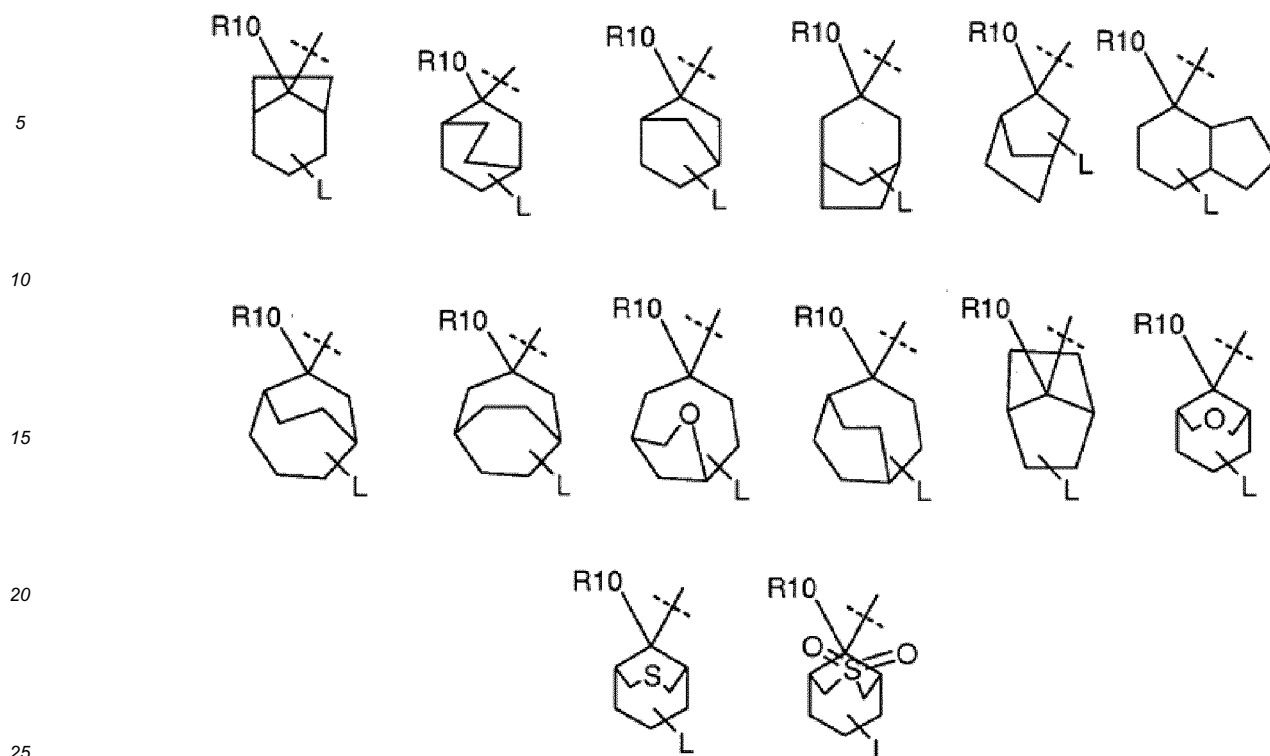
R_7 représente H, un halogène, CN, alkyle (en C_1-C_6), O-alkyle (en C_1-C_6), R' ou SO_2-NH_2 ;

R_8 représente H, un halogène ou alkyle (en C_1-C_6) ;

R_9 représente OH, un halogène, alkyle (en C_6-C_6), $C(O)OH$, $C(O)NH_2$, ou $O-CH_3$, le groupe alkyle (en C_1-C_6) étant non substitué ou substitué ;

R_6 est absent ;

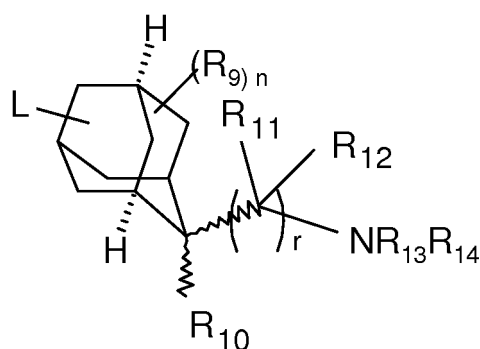
ou est un groupe alkylène (en C_1-C_4) fixé sur le noyau cycloalkyle, le groupe alkylène (en C_1-C_4) formant une deuxième liaison à un atome de carbone différent du noyau cycloalkyle pour former un système de noyau bicyclique de formule



ou, si m et s sont égaux à 2, m est égal à 3 et s est égal à 1, ou m est égal à 4 et s est égal à 0,
 R_6 représente $\text{CH}_2\text{-CH}(\text{CH}_2)_2$ qui est fixé avec un groupe CH_2 au noyau cycloalkyle et les deux autres groupes
 CH_2 sont fixés sur des atomes de carbone différents du noyau cycloalkyle ;

et, si m est égal à 3 et s est égal à 3,

les R_6 sont deux groupes méthylène fixés sur des atomes de carbone différents du noyau cycloalkyle, les
groupes méthylène ou le groupe $\text{CH}_2\text{-CH}(\text{CH}_2)_2$ étant fixés sur des atomes de carbone du noyau cycloalkyle
de manière à former un système adamantane de formule



dans laquelle L peut être fixé sur n'importe quel atome de carbone secondaire ou tertiaire et
dans laquelle le système de noyau bicyclique ou le système adamantane est non substitué ou éventuellement
substitué par R_9 .

R_{10} représente

H, phényle, o-phényle, ou hétéroaryle (en $\text{C}_5\text{-C}_6$),

le groupe phényle ou hétéroaryle (en $\text{C}_5\text{-C}_6$) étant non substitué ou substitué;

R_{11} représente

H,

alkyle (en $\text{C}_1\text{-C}_6$),

alkylène(en $\text{C}_1\text{-C}_6$)- R' ,

cycloalkyle (en $\text{C}_3\text{-C}_8$),

hétéroaryle (en C₅-C₁₀),
 hétérocycloalkyle (en C₃-C₈),
 aryle (en C₆-C₁₀) ;

ou R₁₁ et R₁₂, conjointement avec l'atome de carbone auquel ils sont fixés, forment un noyau cycloalkyle (en C₃-C₈) ou hétérocycloalkyle (en C₃-C₈) ;

R₁₂ représente

alkyle (en C₁-C₆),

cycloalkyle (en C₃-C₈),

hétéroaryle (en C₅-C₁₀),

hétérocycloalkyle (en C₃-C₈), ou

aryle (en C₆-C₁₀) ;

ou R₁₂ représente H, sous réserve que r = 2 et que l'autre radical R₁₂ ne représente pas H ;

ou bien R₁₁ et R₁₂, conjointement avec l'atome de carbone auquel ils sont fixés, forment un noyau cycloalkyle (en C₃-C₈) ou hétérocycloalkyle (en C₃-C₈) ;

R₁₃ et R₁₄ représentent, indépendamment l'un de l'autre

H,

R',

alkyle (en C₁-C₆),

alkylène (en C₁-C₆)-R',

alkylène(en C₁-C₆)-O-alkyle (en C₁-C₆),

alkylène(en C₁-C₆)-O-R',

C(O)alkyle (en C₁-C₆),

C(O)R', ou

C(O)-alkylène(en C₁-C₆)-R',

C(O)N[alkyle (en C₁-C₆)]₂,

R', alkyle (en C¹-C⁶) ou alkylène (en C¹-C⁶) étant non substitués ou substitués, ou

R₁₃ et R₁₄, conjointement avec l'atome de N auquel ils sont fixés, forment un noyau hétérocycloalkyle (en C₃-C₈) non substitué ou substitué ;

n est égal à 0, 1, 2, 3 ou 4 ;

m est égal à 1, 2, 3 ou 4 ;

s est égal à 0, 1, 2 ou 3 ;

r est égal à 1 ou 2 ;

L représente 0, S en NH ;

R' représente

cycloalkyle (en C₃-C₈),

hétéroaryle (en C₅-C₁₀),

hétérocycloalkyle (en C₃-C₈),

aryle (en C₆-C₁₀) ;

dans laquelle, dans les résidus R₃ à R₁₄, le groupe alkyle ou alkylène est non substitué ou éventuellement substitué par un ou plusieurs substituants OH, OCH₃, C(O)OH, C(O)OCH₃, NH₂, NHCH₃, N(CH₃)₂, C(O)NH₂, C(O)NHCH₃ ou C(O)N(CH₃)₂ ;

dans laquelle, dans les résidus R₃ à R₁₄, le groupe cycloalkyle ou hétérocycloalkyle est non substitué ou éventuellement substitué par un ou plusieurs substituants alkyle (en C₁-C₆), halogène, OH, OCH₃, C(O)OH, C(O)OCH₃, NH₂, NHCH₃, N(CH₃)₂, C(O)NH₂, C(O)NHCH₃ ou C(O)N(CH₃)₂ ;

dans laquelle, dans les résidus R₃ à R₁₄, le groupe alkyle ou alkylène est non substitué ou éventuellement substitué par un ou plusieurs substituants halogène ;

dans laquelle, dans les résidus R₃ à R₁₄, les groupes aryle (en C₆-C₁₀) et hétéroaryle (en C₅-C₁₀) sont non substitués ou éventuellement substitués par un ou plusieurs groupes substituants choisis indépendamment parmi halogène,

OH, NO₂, N₃, CN, C(O)-alkyle (en C₁-C₆), C(O)-aryle (en C₆-C₁₀), COOH, COO-alkyle (en C₁-C₆), CONH₂, CONH-alkyle (en C₁-C₆), CON[alkyle (en C₁-C₆)]₂, cycloalkyle (en C₃-C₈), alkyle (en C₁-C₆), alkylène (en C₁-C₆)-NH-alkyle (en C₁-C₆), alkylène (en C₁-C₆)-N-[alkyle (en C₁-C₆)]₂, alcényle (en C₂-C₆), alcynyle (en C₂-C₆), O-alkyle (en C₁-C₆), O-C(O)-alkyle (en C₁-C₆), PO₃H₂, SO₃H, SO₂-NH₂, SO₂NH-alkyle (en C₁-C₆), SO₂N-[alkyle (en C₁-C₆)]₂, S-alkyle (en C₁-C₆) ; SO-alkyle (en C₁-C₆), SO₂-alkyle (en C₁-C₆), SO₂-N=CH-N[alkyle (en C₁-C₆)]₂, SF₅, C(NH)(NH₂), NH₂, NH-alkyle (en C₁-C₆), N[alkyle (en C₁-C₆)]₂, NH-C(O)-alkyle (en C₁-C₆) , NH-C(O)O-alkyle (en C₁-C₆), NH-SO₂-alkyle (en C₁-C₆), NH-SO₂-aryle (en C₆-C₁₀), NH-SO₂-hétéroaryle (en C₅-C₁₀), NH-SO₂-hétérocycloalkyle (en C₃-C₈), N-alkyl(en C₁-C₆)-C(O)-alkyle (en C₁-C₆), N-alkyl(en C₁-C₆)-C(O)O-alkyle (en C₁-C₆), N-alkyl(en C₁-C₆)-C(O)-NH-alkyle (en C₁-C₆), aryle (en C₆-C₁₀), alkylène (en C₁-C₆)-aryle (en C₆-C₁₀), O-aryle (en C₆-C₁₀), O-alkylène(en

C₁-C₆) - aryle (en C₆-C₁₀), hétéroaryle (en C₅-C₁₀), hétérocycloalkyle (en C₃-C₈), alkylène(en C₁-C₆)-hétéroaryle (en C₅-C₁₀), alkylène (en C₁-C₆)-hétérocycloalkyle (en C₃-C₈), O-alkylène(en C₁-C₆)-hétéroaryle (en C₅-C₁₀), O-alkylène(en C₁-C₆)-hétérocycloalkyle (en C₃-C₈),

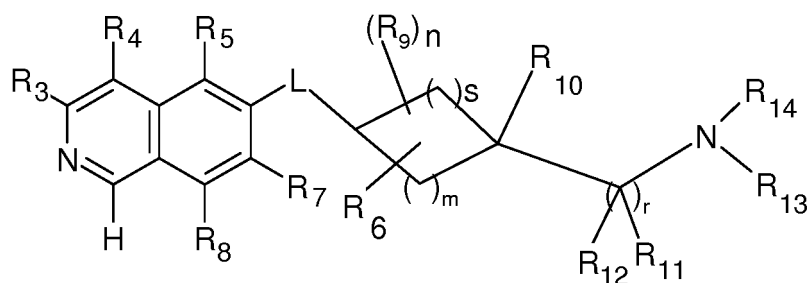
dans laquelle ledit groupe aryle (en C₆-C₁₀), hétéroaryle (en C₅-C₁₀), hétérocycloalkyle (en C₃-C₈) ou cycloalkyle (en C₃-C₈) peut être substitué par un à trois groupes substituants choisis indépendamment parmi un halogène, OH, NO₂, CN, O-alkyle (en C₁-C₆), alkyle (en C₁-C₆), NH₂, NH-alkyle (en C₁-C₆), N[alkyle (en C₁-C₆)]₂, SO₂CH₃, COOH, C(O)O-alkyle (en C₁-C₆), CONH₂, alkylène(en C₁-C₆)-O-alkyle (en C₁-C₆), alkylène(en C₁-C₆)-O-aryle (en C₆-C₁₀) ou O-alkylène(en C₁-C₆)-aryle (en C₆-C₁₀) ; ou

dans laquelle le groupe aryle (en C₆-C₁₀) est substitué en position vicinale par un groupe O-alkylène(en C₁-C₄)-O, ce qui permet de former un noyau à 5-8 chaînons conjointement avec les atomes de carbone auxquels sont fixés les atomes d'oxygène ; et

dans laquelle les substituants aryle des groupes aryle (en C₆-C₁₀), hétéroaryle (en C₅-C₁₀), hétérocycloalkyle (en C₃-C₈) ou cycloalkyle (en C₃-C₈) ne peuvent pas porter d'autres substituants contenant un groupe aryle, hétéroaryle, hétérocycloalkyle ou cycloalkyle (en C₃-C₈) ;

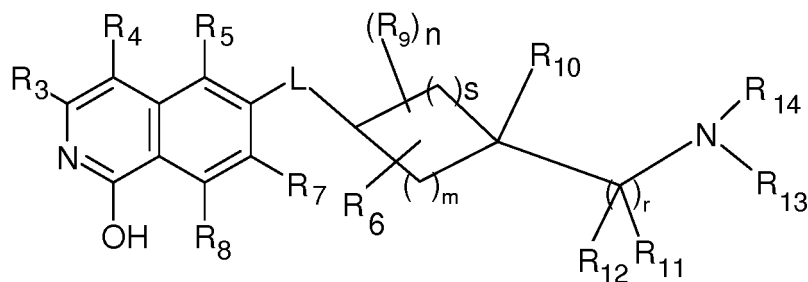
ses formes stéréoisomères et/ou tautomères et/ou ses sels pharmaceutiquement acceptables.

2. Composé de formule (I) selon la revendication 1, dans lequel R₁ représente H et **caractérisé par** la formule (II)



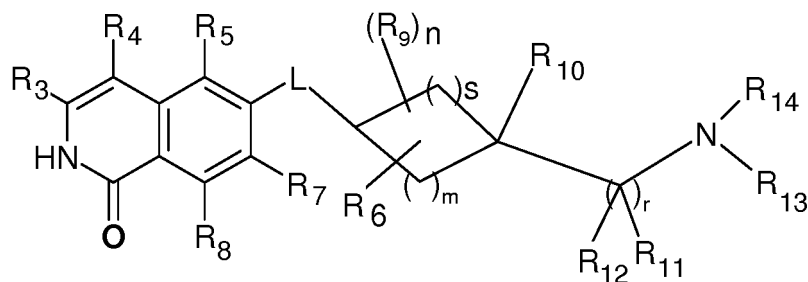
(II)

3. Composé de formule (I) selon la revendication 1, dans lequel R₁ représente OH et **caractérisé par** la formule (IIIa)



(IIIa)

ou la formule (IIIb)



(IIIb)

4. Composé selon la revendication 1, dans lequel R_1 représente NH_2 .
5. Composé selon l'une quelconque des revendications 1 à 4, dans lequel R_3 représente H, halogène, alkyle (en C_1-C_6) ou NHR' , les groupes alkyle (en C_1-C_6) et R' étant non substitués ou substitués.
6. Composé selon l'une quelconque des revendications 1 à 5, dans lequel R_3 représente H.
7. Composé selon l'une quelconque des revendications 1 à 6, dans lequel R_4 représente H, halogène, alkyle (en C_1-C_6) ou alkylène(en C_1-C_2)-phényle, les groupes alkyle (en C_1-C_6) ou phényle étant non substitués ou substitués.
8. Composé selon l'une quelconque des revendications 1 à 7, dans lequel R_4 représente H ou un halogène.
9. Composé selon l'une quelconque des revendications 1 à 8, dans lequel R_5 représente H, halogène, alkyle (en C_1-C_6), aryle (en C_6-C_{10}), cycloalkyle (en C_3-C_8) ou hétéroaryle (en C_5-C_{10}), les groupes alkyle (en C_1-C_6), aryle (en C_6-C_{10}), cycloalkyle (en C_3-C_8) ou hétéroaryle (en C_5-C_{10}) étant non substitués ou substitués.
10. Composé selon l'une quelconque des revendications 1 à 9, dans lequel R_5 représente H.
11. Composé selon l'une quelconque des revendications 1 à 10, dans lequel R_7 représente H, halogène, alkyle (en C_1-C_6), O-alkyle (en C_1-C_6) ou R' , les groupes alkyle (en C_1-C_6) ou R' étant non substitués ou substitués.
12. Composé selon l'une quelconque des revendications 1 à 11, dans lequel R_7 représente H, méthyle ou chloro.
13. Composé selon l'une quelconque des revendications 1 à 12, dans lequel R_8 représente H.
14. Composé selon l'une quelconque des revendications 1 à 13, dans lequel R_9 représente un groupe alkyle (en C_1-C_6) non substitué ou substitué.
15. Composé selon l'une quelconque des revendications 1 à 14, dans lequel R_{10} représente H ou un groupe phényle éventuellement substitué par alkyle (en C_1-C_6), F, Cl, Br, OMe ou CF_3 .
16. Composé selon l'une quelconque des revendications 1 à 15, dans lequel R_{10} représente H.
17. Composé selon l'une quelconque des revendications 1 à 16, dans lequel R_{11} représente H ou méthyle.
18. Composé selon l'une quelconque des revendications 1 à 17, dans lequel R_{12} représente alkyle (en C_1-C_6), dans lequel éventuellement un ou plusieurs atomes d'hydrogène portent des substituants fluoro ; cycloalkyle (en C_3-C_8), hétéroaryle (en C_5-C_6), ou aryle (en C_6-C_{10}), les groupes cycloalkyle (en C_3-C_8), hétéroaryle (en C_5-C_6) ou aryle (en C_6-C_{10}) étant non substitués ou substitués.
19. Composé selon l'une quelconque des revendications 1 à 18, dans lequel R_{12} représente méthyle, éthyle, propyle, isopropyle, cyclopropyle, trifluorométhyle, thiazolyle ou phényle non substitué ou substitué par un groupe alkyle (en C_1-C_4) ou un halogène.

20. Composé selon l'une quelconque des revendications 1 à 18, dans lequel R_{11} et R_{12} forment un noyau cycloalkyle (en C_3-C_8) substitué ou non substitué.

21. Composé selon l'une quelconque des revendications 1 à 20, dans lequel R_{13} et R_{14} représentent, indépendamment l'un de l'autre,

H,

alkyle (en C_1-C_6),

cycloalkyle (en C_3-C_8),

alkylène(en C_1-C_4)-cycloalkyle (en C_3-C_8),

alkylène(en C_1-C_4)-hétéroaryle (en C_5-C_{10}),

alkylène(en C_1-C_4)-hétérocycloalkyle (en C_3-C_8), alkylène (en C_1-C_4) -aryle (en C_6-C_{10}),

alkylène (en C_1-C_6)-O-alkyle (en C_1-C_6),

C(O)-alkyle (en C_1-C_6), ou

R_{13} et R_{14} , conjointement avec l'atome de N auquel ils sont fixés, forment un groupe hétérocycloalkyle (en C_3-C_8),

les groupes alkyle (en C_1-C_6), cycloalkyle (en C_3-C_8), alkylène (en C_1-C_4), hétéroaryle (en C_5-C_{10}), hétérocycloalkyle (en C_3-C_8) ou aryle (en C_6-C_{10}) étant non substitués ou substitués.

22. Composé selon l'une quelconque des revendications 1 à 21, dans lequel

R_{13} représente H ou un groupe alkyle (en C_1-C_6) ; et

R_{14} représente

H,

alkyle (en C_1-C_6),

cycloalkyle (en C_3-C_8),

alkylène(en C_1-C_4)-cycloalkyle (en C_3-C_8),

alkylène(en C_1-C_4)-hétéroaryle (en C_5-C_{10}),

alkylène(en C_1-C_4)-hétérocycloalkyle (en C_3-C_8), alkylène (en C_1-C_4)-aryle (en C_6-C_{10}), ou

alkylène(en C_1-C_4)-O-alkyle (en C_1-C_6),

les groupes alkyle (en C_1-C_6), cycloalkyle (en C_3-C_8), alkylène (en C_1-C_4), hétéroaryle (en C_5-C_{10}), hétérocycloalkyle (en C_3-C_8) ou aryle (en C_6-C_{10}) étant non substitués ou substitués.

23. Composé selon l'une quelconque des revendications 1 à 22, dans lequel

R_{13} représente H, alkyle (en C_1-C_6) et

R_{14} représente H, alkyle (en C_1-C_6) ou cycloalkyle (en C_3-C_8),

les groupes alkyle (en C_1-C_6) ou cycloalkyle (en C_3-C_8) étant non substitués ou substitués.

24. Composé selon l'une quelconque des revendications 1 à 23, dans lequel R_{13} et R_{14} représentent H.

25. Composé selon l'une quelconque des revendications 1 à 24, dans lequel R_6 est absent.

26. Composé selon l'une quelconque des revendications 1 à 25, dans lequel m est égal à 2 et s est égal à 2.

27. Composé selon l'une quelconque des revendications 1 à 26, dans lequel m est égal à 3 et s est égal à 1.

28. Composé selon l'une quelconque des revendications 1 à 27, dans lequel n est égal à 0, 1 ou 2.

29. Composé selon l'une quelconque des revendications 1 à 28, dans lequel n est égal à 0.

30. Composé selon l'une quelconque des revendications 1 à 29, dans lequel r est égal à 1.

31. Composé selon l'une quelconque des revendications 1 à 30, dans lequel L représente S.

32. Composé selon l'une quelconque des revendications 1 à 31, dans lequel L représente NH.

33. Composé selon l'une quelconque des revendications 1 à 32, dans lequel L représente O.

34. Composé selon la revendication 1 choisi dans le groupe constitué par

6-[4-(1-Aminopropyl)-4-(4-fluorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,

6-[4-(1-Amino-cyclopropyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,

6-[4-(1-aminopropyl)-4-phénylcyclohexyl]oxy]-7-chloroisoquinolin-1(2H)-one,
 6-[4-(1-Aminobutyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Aminobutyl)-4-(4-fluorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Aminopropyl)-4-(4-bromo-phényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Aminopropyl)-4-(2-bromo-phényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Aminopropyl)-4-(4-trifluorométhyl-phényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Aminopropyl)-4-(2-fluorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Aminopropyl)-4-(2-chlorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Aminopropyl)-4-phénylcyclohexyloxy]-7-méthyl-2H-isoquinolin-1-one,
 6-[4-(1-Amino-éthyl)-4-(4-fluorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-2-méthyl-propyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-3-méthyl-butyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(Amino-phényl-méthyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-1-méthyl-éthyl)-4-(4-fluorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-cyclopropyl)-4-(2-fluorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-éthyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-1-méthyl-éthyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[amino(cyclopropyl)méthyl]-4-phénylcyclohexyl]-oxy]-7-chloroisoquinolin-1(2H)-one,
 6-[4-(1-Aminopropyl)-4-(4-isopropyl-phényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Aminopropyl)-4-(3-méthoxy)-phényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Aminopropyl)-4-(3-bromo-phényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Amino-2-méthyl-propyl)-4-(4-fluorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, ou 6-[4-(1-Amino-
 propyl)-4-phénylcyclohexyloxy]-4-bromo-7-chloro-2H-isoquinolin-1-one,
 leurs formes stéréoisomères et/ou tautomères et/ou leurs sels pharmaceutiquement acceptables.

- 35.** Composé selon la revendication 1 choisi dans le groupe constitué par
 cis-6-[4-(1-Aminopropyl)-4-(4-fluorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-aminopropyl)-4-(4-fluorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-cyclopropyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Aminopropyl)-4-phénylcyclohexyl]oxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Aminopropyl)-4-phényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Aminobutyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Aminobutyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Aminobutyl)-4-(4-fluorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Aminobutyl)-4-(4-fluorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Aminopropyl)-4-(4-bromo-phényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Aminopropyl)-4-(2-bromo-phényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Aminopropyl)-4-(4-trifluorométhyl-phényl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Aminopropyl)-4-(2-fluorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Aminopropyl)-4-(2-chlorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Aminopropyl)-4-phénylcyclohexyloxy]-7-méthyl-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-éthyl)-4-(4-fluorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Amino-éthyl)-4-(4-fluorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Aminopropyl)-4-(3-bromo-phényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Aminopropyl)-4-(3-bromo-phényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Aminopropyl)-4-(3-méthoxy)-phényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Aminopropyl)-4-(3-méthoxy)-phényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(Amino-phényl-méthyl)-4-(4-fluorophényl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Amino-2-méthyl-propyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Amino-3-méthyl-butyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(Amino-phényl-méthyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 trans-6-[4-(1-Amino-1-méthyl-éthyl)-4-(4-fluorophényl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-cyclopropyl)-4-(2-fluorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-éthyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-1-méthyl-éthyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-[amino(cyclopropyl)méthyl]-4-phénylcyclohexyl]oxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Aminopropyl)-4-(4-isopropyl-phényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-2-méthyl-propyl)-4-(4-fluorophényl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, et

cis-6-[4-(1-Aminopropyl)-4-phénylcyclohexyloxy]-4-bromo-7-chloro-2H-isoquinolin-1-one,
leurs formes stéréoisomères et/ou tautomères et/ou leurs sels pharmaceutiquement acceptables.

36. Composé selon la revendication 1 choisi dans le groupe constitué par

trans-6-[4-((S)-Amino-phényl-méthyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
trans-6-[4-((R)-Amino-phényl-méthyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-((S)-1-Aminopropyl)-4-fluorophénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-((R)-1-Aminopropyl)-4-fluorophénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-((S)-Amino-cyclopropyl-méthyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-((R)-Amino-cyclopropyl-méthyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-((R)-Amino-cyclopropyl-méthyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-((S)-Amino-cyclopropyl-méthyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-((S)-1-Amino-éthyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-((R)-1-Amino-éthyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
6-{4-[(S)-Amino-(4-fluorophényl)méthyl]cyclohexyloxy}-7-chloro-2H-isoquinolin-1-one,
6-{4-[(R)-Amino-(4-fluorophényl)méthyl]cyclohexyloxy}-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-((R)-1-Aminopropyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, et
cis-6-[4-((S)-1-Aminopropyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
leurs formes tautomères et/ou leurs sels pharmaceutiquement acceptables.

37. Composé selon la revendication 1 choisi dans le groupe constitué par

cis-6-[4-(1-Aminopropyl)-4-pyridin-2-yl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-(2,4-difluorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-(4-fluoro-2-méthyl-phényl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-(3,5-difluorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-(3,4-difluorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-o-tolyl-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-(2-trifluorométhoxy-phényl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-(4-fluoro-3-méthoxy-phényl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-(3-éthoxy-phényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-(3-méthoxy-4-méthyl-phényl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-(3,4-difluorophényl)cyclohexyloxy]-7-méthyl-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-(3,5-difluorophényl)cyclohexyloxy]-7-fluoro-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-(3,4-difluorophényl)cyclohexyloxy]-7-fluoro-5-méthyl-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-(3,5-difluorophényl)cyclohexyloxy]-7-méthoxy-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-(2-méthoxy-phényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-(4-trifluoro-méthoxy-phényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-(1-Amino-1-méthyl-éthyl)-4-(4-fluorophényl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-(3,5-difluorophényl)cyclohexyloxy]-4-benzyl-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-(3,5-difluorophényl)cyclohexyloxy]-5-chloro-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-(3,5-difluorophényl)cyclohexyloxy]-5,7-diméthyl-2H-isoquinolin-1-one,
cis-6-[4-(Amino-cyclopropyl-méthyl)-4-(4-fluorophényl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-(3-trifluorométhyl-phényl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-(3-trifluorométhoxy-phényl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-(3-trifluorométhoxy-phényl)-cyclohexyloxy]-7-méthyl-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-(3-trifluorométhyl-phényl)-cyclohexyloxy]-7-méthyl-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-phénylcyclohexyloxy]-7-fluoro-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-phénylcyclohexyloxy]-7-fluoro-5-méthyl-2H-isoquinolin-1-one,
cis-6-[4-(1-Aminopropyl)-4-phénylcyclohexyloxy]-4-benzyl-7-chloro-2H-isoquinolin-1-one,
cis-4-[1-(1-Aminopropyl)-4-(7-chloro-1-oxo-1,2-dihydro-isoquinolin-6-yloxy)cyclohexyl]benzonitrile,
cis-3-[1-(1-Aminopropyl)-4-(7-chloro-1-oxo-1,2-dihydro-isoquinolin-6-yloxy)cyclohexyl]benzonitrile,
6-[cis-4-(1-Aminopropyl)-4-(3-méthanésulfonyl-phényl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
6-[(1S,4S,5S)-5-(1-Aminopropyl)-5-phénylbicyclo[2.2.1]-hept-2-yloxy]-7-chloro-2H-isoquinolin-1-one,
6-[(1R,4R,5R)-5-(1-Aminopropyl)-5-phénylbicyclo[2.2.1]-hept-2-yloxy]-7-chloro-2H-isoquinolin-1-one,
cis-6-[4-(1-Benzylaminopropyl)-4-phénylcyclohexyloxy]-7-méthyl-2H-isoquinolin-1-one,
cis-6-[4-(1-Diéthylaminopropyl)-4-phénylcyclohexyloxy]-7-méthyl-2H-isoquinolin-1-one,
cis-7-Méthyl-6-[4-(1-propylaminopropyl)-4-(3-trifluoro-méthyl-phényl)cyclohexyloxy]-2H-isoquinolin-1-one,
cis-6-[4-(1-Benzylaminopropyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,

cis-7-Chloro-6-[4-(1-isobutylaminopropyl)-4-phényl-cyclohexyloxy]-2H-isoquinolin-1-one,
 cis-6-[4-(1-Butylaminopropyl)-4-phénylcyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-7-Chloro-6-[4-[1-(cyclopropylméthyl-amino)propyl]-4-phénylcyclohexyloxy]-2H-isoquinolin-1-one,
 cis-6-[4-(2-Aminopropyl)-4-(4-fluorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(2-Aminobutyl)-4-(4-fluorophényl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-2-fluoro-éthyl)-4-(4-fluorophényl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 cis-6-[4-(1-Amino-3-méthoxy-propyl)-4-(4-fluorophényl)-cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[3-(1-Aminopropyl)-3-(4-fluorophényl)cyclobutyloxy]-7-chloro-2H-isoquinolin-1-one, et
 6-[3-(1-Aminopropyl)-3-(4-fluorophényl)cyclopentyloxy]-7-chloro-2H-isoquinolin-1-one,
 et leurs formes stéréoisomères et/ou tautomères et/ou leurs sels pharmaceutiquement acceptables.

38. Composé selon la revendication 1 choisi dans le groupe constitué par
 cis-1-[4-(7-Chloro-isoquinolin-6-yloxy)-1-(3,4-di-fluorophényl)cyclohexyl]propylamine,
 cis-1-[4-(7-Bromo-isoquinolin-6-yloxy)-1-(3,4-difluorophényl)cyclohexyl]propylamine,
 cis-1-[1-(3,5-Difluorophényl)-4-(5,7-diméthyl-isoquinolin-6-yloxy)cyclohexyl]propylamine,
 cis-1-[1-(3,5-Difluorophényl)-4-(7-fluoro-5-méthyl-isoquinolin-6-yloxy)cyclohexyl]propylamine,
 cis-1-[1-(3,4-Difluorophényl)-4-(7-fluoro-isoquinolin-6-yloxy)cyclohexyl]propylamine,
 cis-1-[4-(7-Chloro-isoquinolin-6-yloxy)-1-(3,5-difluorophényl)cyclohexyl]propylamine,
 cis-1-[4-(5-Chloro-isoquinolin-6-yloxy)-1-(3,5-difluorophényl)cyclohexyl]propylamine,
 cis-1-[4-(7-Chloro-isoquinolin-6-yloxy)-1-phénylcyclohexyl]propylamine,
 cis-1-[4-(5,7-Diméthyl-isoquinolin-6-yloxy)-1-phénylcyclohexyl]propylamine,
 cis-1-[4-(7-Fluoro-isoquinolin-6-yloxy)-1-phénylcyclohexyl]propylamine,
 cis-1-[4-(5-Chloro-isoquinolin-6-yloxy)-1-phénylcyclohexyl]propylamine,
 cis-1-[4-(7-Fluoro-5-méthyl-isoquinolin-6-yloxy)-1-phénylcyclohexyl]propylamine,
 cis-1-[4-(7-Bromo-isoquinolin-6-yloxy)-1-phénylcyclohexyl]propylamine,
 cis-1-[4-(7-Méthyl-isoquinolin-6-yloxy)-1-phénylcyclohexyl]propylamine,
 cis-6-[4-(1-Aminopropyl)-4-phénylcyclohexyloxy]-7-chloro-isoquinolin-1-ylamine,
 [4-(1-Aminopropyl)-4-(4-méthoxy-phényl)cyclohexyl]isoquinolin-6-yl-amine, et
 1-Amino-[4-(1-aminopropyl)-4-(4-méthoxy-phényl)cyclohexyl]isoquinolin-6-yl-amine,
 et leurs formes stéréoisomères et/ou tautomères et/ou leurs sels pharmaceutiquement acceptables.

39. Composé selon la revendication 1 choisi dans le groupe constitué par
 6-[4-(1-Amino-1-phényl-éthyl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[Amino-(4-méthoxy-phényl)méthyl]cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[Amino-(4-fluorophényl)méthyl]cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(Amino-p-tolyl-méthyl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, ou
 6-[4-(Amino-phényl-méthyl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 et leurs formes stéréoisomères et/ou tautomères et/ou leurs sels pharmaceutiquement acceptables.

40. Composé selon la revendication 1 choisi dans le groupe constitué par
 6-[4-[1-Amino-1-(4-fluorophényl)éthyl]cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[1-Amino-1-(4-méthoxy-phényl)éthyl]cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[1-Amino-1-cyclopentyl-éthyl]cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[1-Amino-1-éthyl-propyl]cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[1-Amino-1-cyclopropyl-éthyl]cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-[1-Amino-1-n-propyl-éthyl]cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 6-[4-(1-Aminopropyl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one, et
 6-[4-(Amino-cyclopropyl-méthyl)cyclohexyloxy]-7-chloro-2H-isoquinolin-1-one,
 et leurs formes stéréoisomères et/ou tautomères et/ou leurs sels pharmaceutiquement acceptables.

41. Composé de formule (I) et/ou son sel pharmaceutiquement acceptable selon l'une quelconque des revendications 1 à 40 pour une utilisation comme médicament.

42. Composé de formule (I) et/ou un de ses sels pharmaceutiquement acceptables selon l'une quelconque des revendications 1 à 40 pour utilisation dans le traitement et/ou la prévention de l'hypertension, de l'hypertension pulmonaire, de l'hypertension oculaire, de la rétinopathie, du glaucome, des troubles circulatoires périphériques, des artériopathies oblitérantes (PAOD), de l'insuffisance coronarienne, de l'angine de poitrine, de l'hypertrophie cardiaque, de l'insuffisance cardiaque, des maladies ischémiques, de l'insuffisance ischémique d'un organe (atteintes aux organes

cibles), de la fibrose du poumon, de la fibrose du foie, de l'insuffisance hépatique, de la néphropathie, de l'insuffisance rénale, de la fibrose du rein, de la glomérulosclérose rénale, de l'hypertrophie d'un organe, de l'asthme, de la bronchopneumopathie chronique obstructive (COPD), du syndrome de détresse respiratoire de l'adulte, des troubles thrombotiques, de l'A.V.C., du vasospasme cérébral, de l'ischémie cérébrale, de la douleur, de la dégénérescence neuronale, des lésions de la moelle épinière, de la maladie d'Alzheimer, de la naissance prématurée, de la dysfonction érectile, des dérèglements endocriniens, de l'artériosclérose, de l'hypertrophie de la prostate, du diabète et des complications du diabète, du syndrome métabolique, de la resténose des vaisseaux sanguins, de l'athérosclérose, de l'inflammation, des maladies auto-immunes, du SIDA, des ostéopathies, de l'infection des voies digestives par des bactéries, de la septicémie ou de la propagation et de l'évolution du cancer.

43. Composé de formule (I) et/ou un de ses sels pharmaceutiquement acceptables selon l'une quelconque des revendications 1 à 40 pour utilisation dans le traitement et/ou la prévention de l'hypertension, de l'hypertension pulmonaire, de la fibrose du foie, de l'insuffisance hépatique, de la néphropathie, de l'insuffisance rénale, de la bronchopneumopathie chronique obstructive (COPD), du vasospasme cérébral, de la douleur, des lésions de la moelle épinière, de la dysfonction érectile, de la resténose des vaisseaux sanguins ou de la propagation et de l'évolution du cancer.

44. Composé de formule (I) et/ou un de ses sels pharmaceutiquement acceptables selon l'une quelconque des revendications 1 à 40 pour utilisation dans des approches curatives associées à un traitement par des cellules souches ou des cellules souches multipotentes induites, pour l'amélioration de la reconnaissance ou dans le traitement ou la prévention de la dépression, de l'épilepsie, de la fibrose du cœur, de la nécrose médullaire rénale, des dysfonctions tubulo-interstitielles, de la sclérose en plaques, de la sténose des vaisseaux ou des dyslipémies.

45. Médicament comprenant une quantité efficace d'au moins un composé de formule (I) et/ou d'un de ses sels pharmacologiquement acceptables selon l'une quelconque des revendications 1 à 40, des excipients et véhicules pharmaceutiquement tolérés et, le cas échéant, d'autres additifs et/ou d'autres ingrédients actifs.

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